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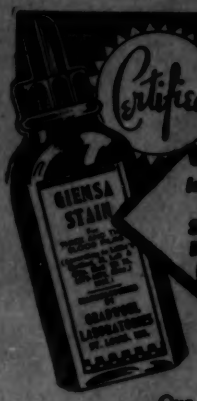

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ANNALS OF
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CONVALESCENCE: A STUDY IN THE PHYSIOLOGICAL RECOVERY OF NITROGEN METABOLISM AND LIVER FUNCTION *

By ROBERT W. KEETON, F.A.C.P., WARREN H. COLE, NATHANIEL CALLOWAY, NATHANIEL GLICKMAN, H. H. MITCHELL, J. DYNIEWICZ and D. HOWES, *Chicago, Illinois*

CONVALESCENCE embraces the recovery of a multitude of physiological processes in an individual who has suffered from trauma, disease, or an operation. These various physiological processes recover at different rates and the recovery of many is not manifested by any marked objective or subjective signs. There finally comes a time when the patient is conscious of his return to normal and is again ready for work. This transformation from illness to health is often dramatic and is frequently not accompanied by any sign which the physician can detect. The study of convalescence is concerned with the analysis of these disturbances in physiology and an assay of the methods by which recovery can be hastened. The present discussion deals largely with convalescence as illustrated by patients submitted to herniorrhaphy, and is confined to the recovery of nitrogen metabolism and liver function. The general plan of the study and many of the detailed data have been presented elsewhere.[1] Some of the conclusions have appeared also in abstract form.[2]

THE NITROGEN METABOLISM

The negative nitrogen balance which occurs in fractures and after osteotomy has been attributed to excess catabolism.[3, 4] In the period immediately following the fracture, the intake of food was inadequate and so

* Presented before the meeting of the American College of Physicians, Chicago, May 2, 1947.

From the Departments of Medicine and Surgery, Chicago, and the Division of Animal Nutrition, Urbana, University of Illinois.

The experimental data reported in this paper were secured in the course of a project covered by a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

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the metabolic studies were postponed a few days. This depletion of the protein stores would influence the subsequent metabolic periods. Cuthbertson has shown that the oxygen consumption was also increased. This should account for some of the nitrogen loss in Howard's cases, since they were fed relatively low caloric diets in some of the subsequent periods. However, the persistence of the nitrogen losses over longer periods in the case of fractures, and shorter ones in osteotomies, supports Cuthbertson's view that an increased catabolism exists. His work also supports the view that the extra nitrogen is derived from the muscles and not from the local site of injury. The derangement of the nitrogen metabolism in the "alarm reaction" with its increased nitrogen metabolism during the first phase of the general adaptation syndrome (Hans Selye [5]) has been advanced as an explanation for nitrogen losses in injuries and postoperative states. Increased excretion of adrenal corticoids may occur on exposure to low atmospheric pressures with its anoxia,[6] and might well be responsible for increased gluconeogenesis and nitrogen loss. The view that adrenal activity plays a rôle in nitrogen excretion and its wastage is supported by a number of studies,[7] which have shown an increased output of urinary corticoids in previously healthy subjects subjected to trauma or infection. The behavior of "debilitated" patients in the presence of infection is in sharp contrast. These patients may exhibit a storage of nitrogen and a low to normal output of urinary cortin. Browne et al.[7a, b] contend that the feeding of high protein and high caloric diets may mitigate or even overcome the negative nitrogen balance but it does not overcome or prevent the catabolic process. The period during which this anomaly occurs is designated the "catabolic period."

In certain acute infections, especially meningitis and postoperative states, Grossman et al.[8] have observed similar losses of nitrogen persisting for a considerable time after the acute phase of the disease had subsided. The protein intake was greatly increased, but it did not perceptibly influence the nitrogen balance. Earlier Peters [9] had emphasized the ability of the poorly nourished individual to conserve protein and attain nitrogen equilibrium in conditions under which the better nourished individual fails. He suggests that there may be a failure in synthesis of proteins and that this varies directly with the severity of the injury and inversely as the state of nutrition. This viewpoint of the failure in synthesis is supported by Albright.[7c] If further work should confirm the existence of a period of irreparable nitrogen loss, then a method of assaying the immediate severity of an operative procedure or an injury would be available.

On the contrary, the negative nitrogen balances seen in postoperative patients are often due to a disregard for well established nutritional rules which, if applied, would prevent the negative balances.[7c] Positive nitrogen balances have been maintained after gastric resections and other operations.[10]

It has been shown (Strang,[11] Keeton [12]) that obese patients subsisting on diets below their caloric requirements, which contain adequate quantities of

protein, use their body fat to replace their caloric deficit without disturbing their metabolism. Thus such patients can store nitrogen, maintain normal metabolic rates [13] and a minimal nitrogen excretion of 2 to 3 gm. on diets containing calories 30 to 60 per cent below their basal requirements. They show no signs or symptoms of starvation. On the contrary, their sense of well being is increased. If the subject whose stores of fat vary little from normal, as shown by expected weights in actuarial tables, is subjected to a similar diet containing his basal requirements, he will over a period of time develop a negative nitrogen balance, lowered basal metabolic rate, and other changes associated with starvation (Benedict,[14] Lusk [15]). If the starvation is pushed to a point at which there has been a 25 per cent weight loss (Keys [16]), then the stores of body fat have been reduced 60 per cent and the "tissues" 41 per cent. The fat is unable to protect the body protein and some is retained despite increasing tissue losses. It would be expected that the obese individual and the individual with normal stores of body fat would react as they do normally when convalescing from a surgical procedure. However, this will have to be determined experimentally. It would also be of great practical importance to know the amount of body fat required to protect the nitrogen. These problems are now under study.

Our subjects (figure 1) were normal in body build as shown by their percentage deviation from actuarial standards. A practical clinical rule in-

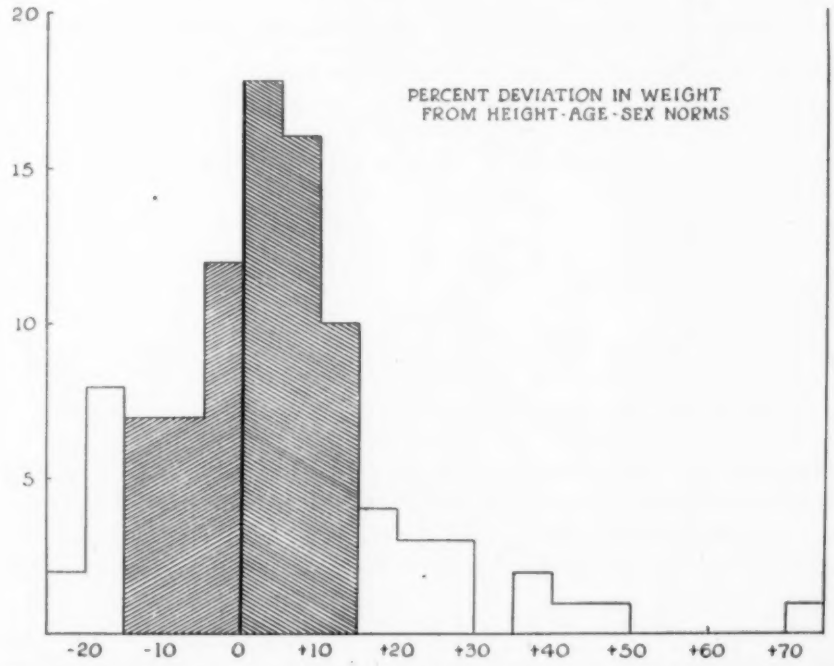

FIG. 1. Distribution of 95 patients submitted to herniorrhaphy, based on the percentage deviation in weight from normal, according to actuarial standards. Ordinate, number of patients; abscissa, per cent deviation.

dicates that obesity begins when the patient is 15 per cent overweight and leanness when he is 15 per cent underweight. By this definition 70 out of 95 patients were normal as to weight. Most of the patients were furnished by selective service boards for correction of their hernias and 85 per cent of these patients were below 47 years of age. They were physically active prior to their entrance to the hospital. Their stores of nitrogen were normal, as shown by the readiness with which they attained nitrogen equilibrium preoperatively. Their body fat would not furnish any significant protection to their body proteins. The herniorrhaphy is to be regarded as a sudden interruption to their normal physiological process. Any observed alterations are to be attributed to the operation and it is to be anticipated that a complete restoration in function would occur. Thus all the conditions for a satisfactory clinical experiment are fulfilled.

In table 1 is found a description of the managements of the groups fed by tube. The feeding through the tube was continued to six hours before

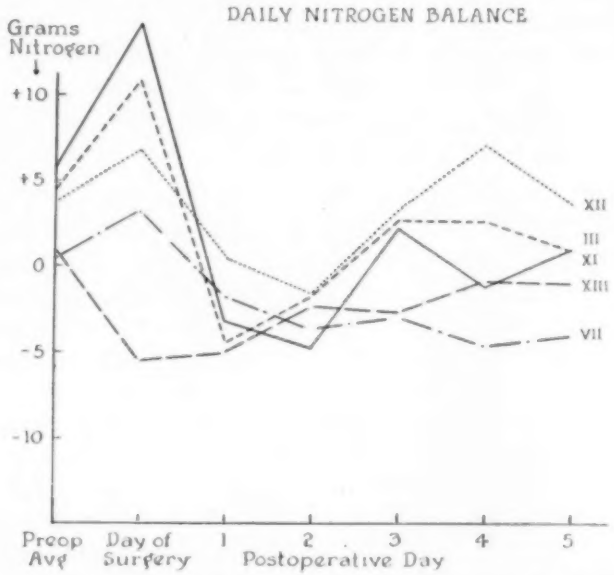

FIG. 2. Average daily nitrogen balance for the groups fed by tube.

the operation and resumed six hours after the operation. This prevented any significant interruption to the nutrition. The courses of the nitrogen balances are depicted in figure 2. In table 2 is found the description of the managements of the groups fed orally. The courses of their nitrogen balances are depicted in figure 3.

The groups (III, XI, XII, VII) which received from 2.75 to 1.21 gm. of protein per kilogram body weight retained from 3 to 14 gm. of nitrogen on the day of operation. By the end of the first or second postoperative days they had lost all of this nitrogen, and on the average, an additional 3.9 gm.

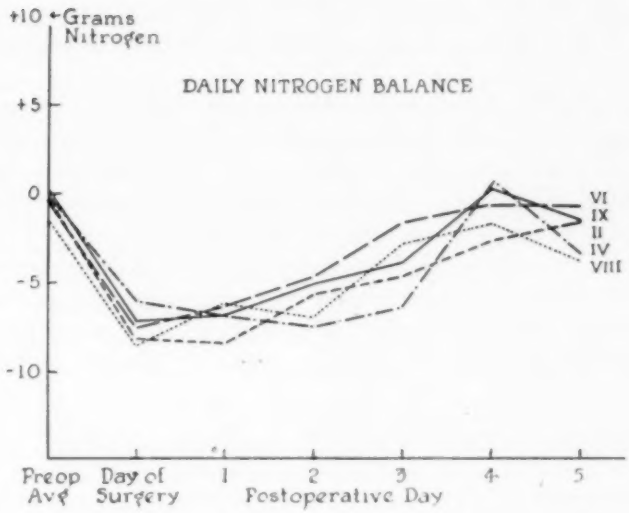

FIG. 3. Average daily nitrogen balance for the groups fed orally.

TABLE I

Description of Management of Groups Fed by Tube* Including Nitrogen Balance on Day of Operation and Five Succeeding Days (see Figure 2)

Group No.	Number of Patients	Daily Calories	Protein		Ambulation	Nitrogen Balance
			Calories Per Cent	gm./kg.		
III†	5	B+100%	20	2.64	+	+10.2
XI	7	B+20%	40	2.70	0	+ 7.6
XII	5	B+20%	40	2.75	+	+19.4
VII	6	B+20%	15	1.21	0	−13.8
XIII‡	3	B+100%	Level Group VII	1.21	0	−17.5

* Anesthesia: Nitrous oxide induction with ether maintenance in all groups.

† Supplements to diet:

(*a*) Preoperatively daily: Orally, choline—1.5 gm., vitamin B complex from yeast—2 tablets 3 times a day, ascorbic acid—200 mg., vitamin A—5000 i.v., vitamin D—500 i.v.

(*b*) Day of operation: Orally, choline—1.5 gm., methionine—1 gm. Intravenously, 5 per cent amigen solution in 5 per cent glucose (2000 c.c.). Parenterally, vitamin K—4 mg., liver extract (2 units to 1 c.c.)—5 c.c., adrenal cortical extract—5 c.c., testosterone propionate—10 mg., thiamine chloride—10 mg., riboflavin—10 mg., pyridoxine—5 mg., calcium pantothenate—50 mg., nicotinamide—250 mg., ascorbic acid—200 mg.

(*c*) Four succeeding postoperative days: Same supplements as in (*b*) with omission of methionine and amigen solution.

‡ Feeding schedule group XIII:

Preoperatively, 5th and succeeding postoperative days—protein at same level as group VII, calories, B + 100 per cent.

Day of operation and 1st, 2nd, 3rd, 4th postoperative days—protein levels 0: 0.3: 0.6: 0.9: 1.21 gm. per kg., respectively, calories B + 100 per cent.

The groups (II, IV, VI, VIII, IX) which received no protein and only 50 gm. of glucose by vein lost on the average the day of operation 7.4 gm. of nitrogen.

The group (XIII) which received no protein but basal calories plus 100 per cent, composed of carbohydrate and fat, lost an intermediate amount of nitrogen, 5.5 gm. on the day of operation. The groups receiving protein and maintenance or excessive calories developed a smaller negative balance immediately and returned to a balance more quickly.

However, it would seem that when protein in normal to increased amounts is fed, there is an interference with its retention. If one calculates the average drop from the preoperative levels to the lowest level on either the first or second postoperative days, a value of 7.0 gm. will be obtained.

TABLE II

Description of Management of Groups Fed Orally* Including Nitrogen Balance on Day of Operation and Five Succeeding Days (see Figure 3)

Group No.	Number of Patients	Daily Calories	Protein		Ambulation	Nitrogen Balance
			Calories Per Cent	gm./kg.		
II	10	B+20%	15	1.21	0	−31.4
IV†	6	B+20%	15	1.21	0	−31.3
VI	9	B+20%	15	1.21	+	−21.3
VIII‡	7	B+20%	15	1.21	0	−29.8
IX§	4	B+20%	15	1.21	0	−24.3

* Feeding schedule for all groups:
(*a*) Preoperatively, 5th and succeeding postoperative days total diet eaten as indicated.
(*b*) Day of operation, parenteral glucose—50 gm.; protein 0; fat 0.
(*c*) Four succeeding days, 1/4, 1/2, 3/4, 4/4 of preoperative diet, respectively.
† Anesthesia spinal: In all other groups nitrous oxide induction with ether maintenance.
‡ Supplements same as group III (table 1) plus 4 mg. vitamin K throughout hospital stay.
§ Methionine 2.0 gm. daily during hospital stay.

This is approximately the same as that obtained (7.4 gm.) in groups receiving no protein. This behavior could be attributed to an increase in the catabolism of the protein (Cuthbertson [8]) or an abeyance in protein synthesis (Peters [9]). The protein has been used for energy purposes but the nitrogen excretion has lagged 24 hours. The period within which this alteration occurs corresponds to the "catabolic period" of Browne and his associates. From a study of figure 2, it would seem that this alteration extended over the day of operation, the first and second postoperative days in those patients (table 1) receiving normal to increased amounts of protein. In the case of those patients receiving no protein on the day of operation and gradually increasing quantities over the next four days (table 2, figure 3; group XIII, figure 2), there was a prompt drop in the nitrogen excretion on the day of operation. However, the gradually increasing amounts of protein given on the succeeding four days were retained. In a herniorrhaphy the disturbance in the nitrogen metabolism has probably passed by

the first and certainly by the second postoperative days. Thereafter the organism functions normally. This time corresponds to the period within which an increased output of cortin was noted by Shipley et al.[7d] following herniorrhaphy. It would be expected that if the operative trauma were greater, the disturbance in nitrogen metabolism would last longer.

Group XIII which received excessive calories but the same amount of protein as the orally fed groups retained nitrogen more readily and over the six day period lost less (17.5 gm.) than the average of the other groups (27.6 gm.), which received basal calories plus 20 per cent or less. This conservation of nitrogen by the ingestion of extra calories is the expected normal response.

The comparison of groups XI and VII is instructive. Each received basal calories plus 20 per cent. Group XI which received 2.7 gm. of protein per kilo promptly returned to a positive balance of 7.6 gm. for the period while group VII which received 1.2 gm. per kilo showed a negative balance of 13.8 gm. for the period. This would indicate that on a maintenance diet an increase in the proportion of calories from protein is an important factor in reëstablishing nitrogen balance and restoring depleted protein stores. Similar conclusions were reached by Werner [10e] in his studies on patients undergoing subtotal gastrectomies for peptic ulcer.

Group IX, which was fed 2 gm. of methionine daily, showed a negative nitrogen balance of 24.3 gm. as compared with the average balances of groups II, IV, and VIII (30.8 gm.). Group VI is omitted from the comparison because ambulation was a part of the management. This decrease in the negative nitrogen balance is not significant.* No influence of the methionine was noted in decreasing the negative nitrogen balance on the day of operation.

Convalescence as applied to nitrogen metabolism includes not only the attainment of nitrogen equilibrium, but also the repletion of the protein stores. Thus equilibrium may be attained and maintained in the face of a deficit in protein stores (Martin and Robison [17]). The slowness with which the nitrogen stores are reconstituted in subjects submitted to low protein diets and to short periods of starvation with or without added carbohydrate has been studied by Kenyon.[18] On refeeding nitrogen equilibrium was attained in six to eight days, but the repletion of the protein stores required a period of three to four weeks' time. Additional calories derived from protein facilitated this repletion, but those derived from carbohydrate were not so effective. In the rehabilitation of normal subjects subjected to relatively severe semi-starvation (Keys et al.[16]) the "tissues" were not completely rehabilitated after 32 weeks. Early in the rehabilitation it seemed advantageous to increase the proportion of the calories derived from protein. The prevention of any significant negative nitrogen balance, even though it should last for only a short time, would be highly desirable.

* Student's [40, 41] method and tables designated for determining the significance of the mean of a small series of paired differences were used. All data were treated statistically.

Creatine and Creatinine Excretion. The creatine excretions (table 3) of patients in group III who received 2.6 gm. of protein per kilo were significantly greater ($P = 0.020$) than those of patients in groups I, II, and V, who received 1.21 gm. per kilo. This comparison was made on creatine excretions obtained prior to the operation. The difference is attributed to the quantity of meat in the diet.

TABLE III

Creatine Excretion
Effect of Quantity of Protein and Herniorrhaphy

Comparison			Results	
Number	Groups	Periods	Excretion	Probability
1	III* vs. I,† II and V‡	Preoperative	Higher in III	0.020
2	I, II and V vs. I, II and V	Preoperative vs. Day of operation	Decreased	<0.0005
		Preoperative vs. 1st postoperative day	Decreased	0.025
		Preoperative vs. Succeeding postoperative days	Unchanged	—
3	III vs. III	Preoperative vs. Day of operation	Unchanged	—
		Preoperative vs. Succeeding postoperative days	Unchanged	—

* Diet see table 1.
† Regular diet served on surgical ward.
‡ Diet same as group IV, see table 2.

On the day of operation and the four succeeding days the patients in group III received daily injections of 10 mg. of testosterone propionate. Wilkins and Fleischman [19] have shown that testosterone does not produce a creatinuria. Consequently the effects of this procedure can be eliminated from consideration. When the preoperative excretion of creatine in group III was compared with the postoperative excretion, no significant change was noted.

In the members of groups I, II, and V who received much less meat as well as other proteins (day of operation no protein, and first postoperative day 0.3 gm. per kilo) the creatine excretion on these two days was significantly lower ($P < 0.0005$ and $= 0.025$, respectively) than the preoperative

excretion. Since there is considerable variation in the individual excretion of creatine, each patient was compared with himself and the probability computed on this basis. Unless the operation mobilized an endogenous supply of creatine this decrease would be expected.

When the creatinine excretions were studied in a similar manner in group III with high protein intake and in groups IV and V with low protein intake, it was found that herniorrhaphy produced no alterations in the excretions. The wastage of nitrogen, which occurred on the day of herniorrhaphy and two succeeding days in patients receiving by tube diets with normal to increased quantities of protein, did not involve the creatine and creatinine metabolism. The significant decrease of creatine rather than an increase on the day of operation and the succeeding day in patients on diets with low quantities of meat and other proteins and low calories would imply that there was no disturbance in muscle metabolism produced by herniorrhaphy.

Influence of Ambulation on Nitrogen Balance

Taylor et al.[20] have shown that in the normal subject at bed rest a negative nitrogen balance accompanied by a reduced blood volume occurred. With reconditioning the nitrogen balance became positive and the blood volume increased. An increased nitrogen output has been noted during the immobilization of healthy subjects in casts.[21] This output decreased during the recovery period and storage occurred. In a second study [22] two of the previous subjects were immobilized in casts, but placed on an oscillating rather than fixed bed. The nitrogen losses were less. The stiffness of the joints and aching of muscles also were less.

There are four groups which may be used for a study of the effect of ambulation on nitrogen balance. Two of these, VI and II, received the same diets (B + 20 per cent) orally, but differed from each other by the addition of ambulation to the management of group VI. These diets contained relatively small amounts of protein during the periods of comparison. Comparison 1, table 4, shows that ambulation very probably decreased the negative nitrogen balance. Groups XII and XI were tube fed with diets high in protein which contained the basal calories plus 20 per cent. Comparison 2 shows no significant difference between the groups. It is probable that the increased protein in the diet masked any effects of ambulation. In comparison 3 the comparable groups with ambulation are contrasted with those receiving no ambulation. However, the type of diets and their methods of administration were entirely different. Consequently the data would be considered as heterogeneous and, therefore, were subjected to an analysis of variance. By this method the data do not indicate a significant difference between ambulated and non-ambulated patients although a considerable probability may be considered to have been established that ambulation does improve the nitrogen balance of a patient convalescing from surgery.

TABLE IV

Effects of Ambulation on Nitrogen Balance Including Day of Operation and Five Succeeding Days

Comparison	Group Numbers	Number of Patients	Ambulation	Nitrogen Balance	Probability*
1	VI	6	+	−21.3	0.036
	vs.				
	II	10	0	−31.4	
2	XII	5	+	+19.4	Insignificant
	vs.				
	XI	7	0	+ 7.6	
3	VI and XII	11	+	− 1.9	0.058
	vs.				
	II and XI	17	0	−23.8	

* The probability favors first group or groups.

Influence of Infection on Nitrogen Metabolism. Surgical procedures in general are accompanied by a rise in temperature. There are many factors which combine to produce these clinically non-significant rises. There is absorption from the devitalized tissues. There may be small areas of patchy atelectasis which reëxpand and drain during the first 24 to 36 hours or there may be some disturbance in the fluid and electrolyte balance. The

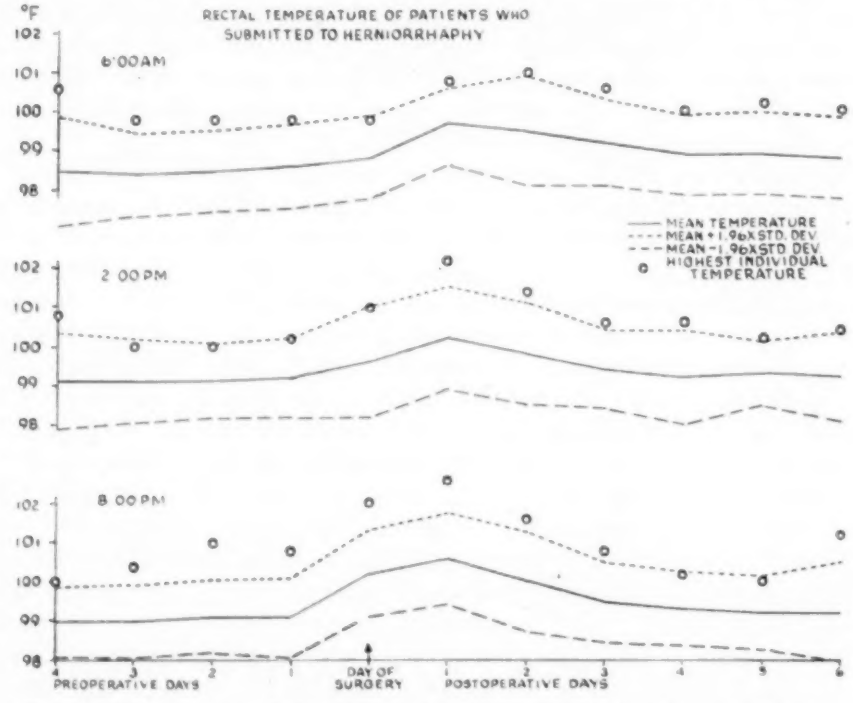

FIG. 4. Daily mean variations in rectal temperatures of 97 patients submitted to herniorrhaphy.

temperature pattern varies with the operation. In order to secure this pattern for herniorrhaphies performed under spinal or general anesthesia (nitrous oxide and ether) an analysis was made of the 97 cases (figure 4) whose postoperative courses showed no complications. On either side of the mean are lines drawn which represent the mean $\pm$ 1.96 $\times$ standard deviation. The chance variations of temperature which are inherent in the operative procedure should fall within the lines. Temperatures which fall outside could be due to an unusual variation in the procedure, or to the introduction of a new factor. It will be noted that the individual variations are few in number and occurred commonly at 8 p.m. both before and after the operation. Perhaps a further word should be added concerning the distinction between the clinically non-significant temperatures described above and those associated with frank infection. In the former the local defenses are operative and the infection is under control. In the latter the infection has escaped from control and the general "alarm reaction" with its accompanying physiological adjustments has been activated.

Any definite elevation of the rectal temperature above this pattern was considered significant and attributed to a complicating infection. Seven such cases occurred in our series. When the nitrogen balance of these seven patients were computed for the day of surgery and the five succeeding days, it was found that they were in marked negative balance as compared with the control members of their groups, who did not suffer from infection. They lost 165.7 extra grams of nitrogen over the average amount lost by their 34 corresponding controls during the same period.

In figure 5 the responses to herniorrhaphy of the control members of group II are shown. These subjects received postoperatively a diet which contained a reduced intake of calories and protein. The calories (basal + 20 per cent) are expressed in terms of the basal requirements, and nitrogen in grams. They received on the day of operation 200 calories as intravenous glucose and no protein, on succeeding days ¼, ½, ¾, and ¾ of their preoperative diet. They approximated nitrogen balance on the fifth postoperative day. The 6 a.m. temperature elevations and the efficiency of the liver as measured by the urobilinogen excretion are shown.

In figure 6 is shown the behavior of a patient (J. T.) of group IX who developed a severe wound infection. His temperature was higher and persisted to the tenth postoperative day. The efficiency of his liver as indicated by the urobilinogen excretion was definitely reduced. These findings attest to the severity of the infection. His showing was obviously poorer than the control group. His nitrogen output remained high and the negative nitrogen balance continued as long as the infection remained uncontrolled. He was given protein hydrolysate intravenously on the day of operation and ate all of his prescribed diet thereafter. After the fourth day the diet contained borderline maintenance calories. It is interesting to note that the output of nitrogen paralleled the curve of urobilinogen excretion.

Figure 7 shows the behavior of a patient (L. G.) who developed a postoperative atelectasis. His diet contained much more protein than that of patient J. T. and he received more calories since he was tube fed. His nitrogen balance remained sharply negative until the atelectasis was relieved

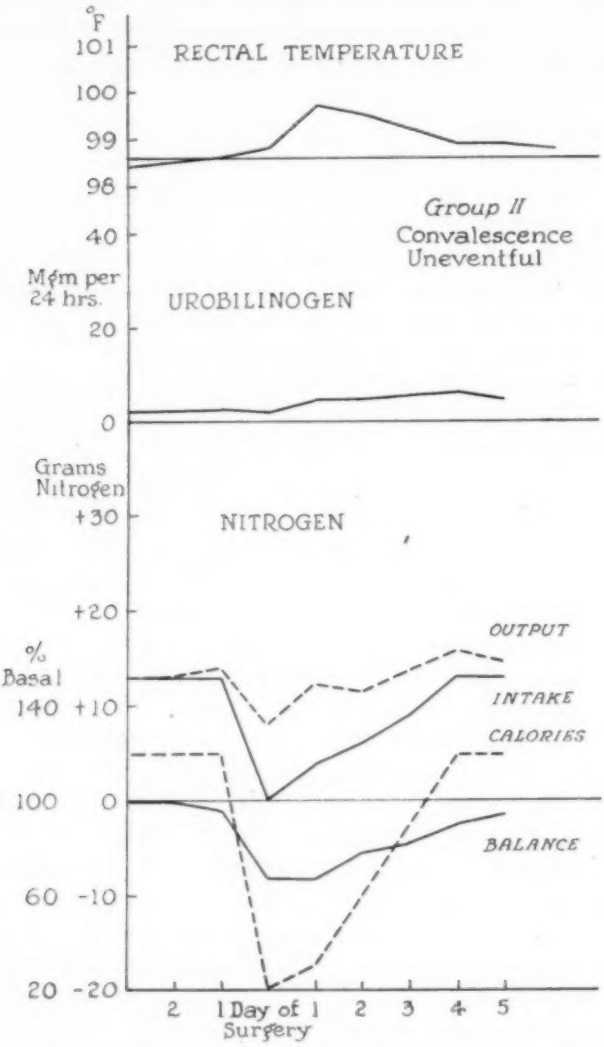

FIG. 5. Average responses of the 10 members of group II who experienced an uneventful convalescence.

and the temperature subsided. The findings in two other cases (L. R. with a pneumonitis and J. K. with a wound infection) corroborate those discussed. In the face of an infection the subjects eat poorly so that it is difficult to determine whether the addition of extra calories would overcome the negative balance or not. It is clear that the subject with an infection

loses more nitrogen than his control, and that an increase in the calories derived from protein does not correct the defect. The nitrogen wastage disappears with the control of the infection.

It would seem likely that the effects of infection and operative procedures on patients are similar and are probably induced by the same mechanisms.

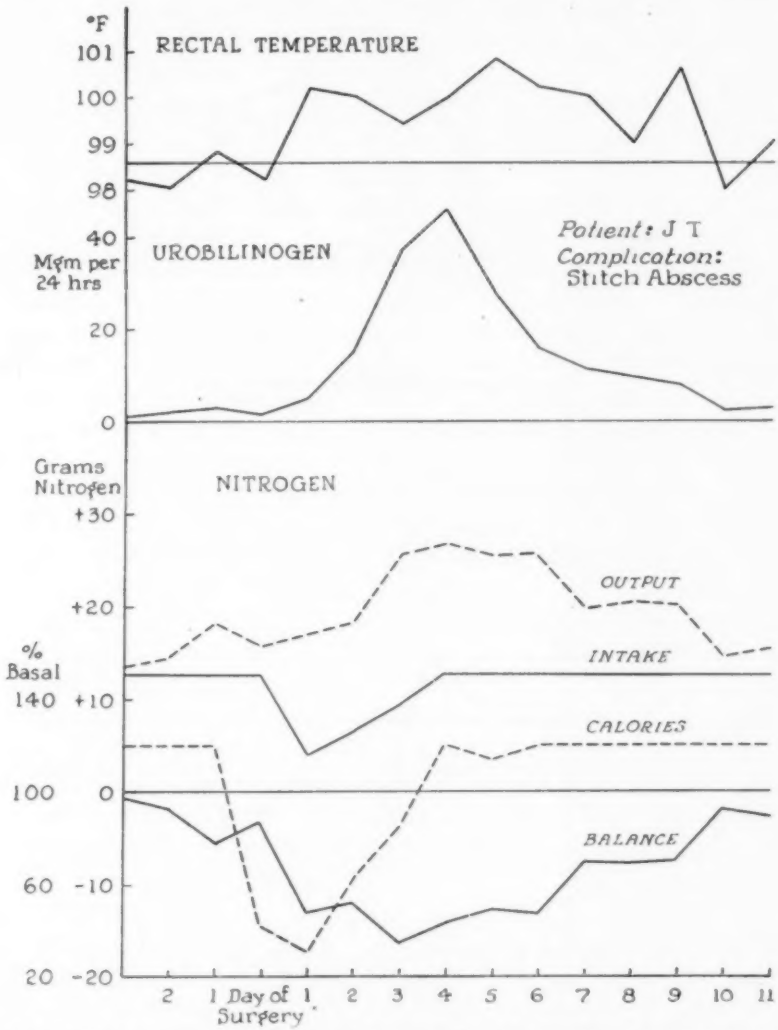

FIG. 6. The responses of a member of group II who developed a stitch abscess.

Further evidence for this view has been furnished by Mann et al.[23] They have reported that the amino acid nitrogen of the blood falls abruptly after injury, operative procedures, and infection. It remains low until recovery is well advanced, even while nitrogen catabolism is greatly increased by the administration of high protein diets. According to Whipple and

associates [24] there is a continuous flow of plasma protein out of the circulation into the tissues and vice versa. The condition is described as a "dynamic equilibrium." That this flow of plasma protein results in the rapid exchange of its constituent amino acids has been shown by Fink.[25] Lysine

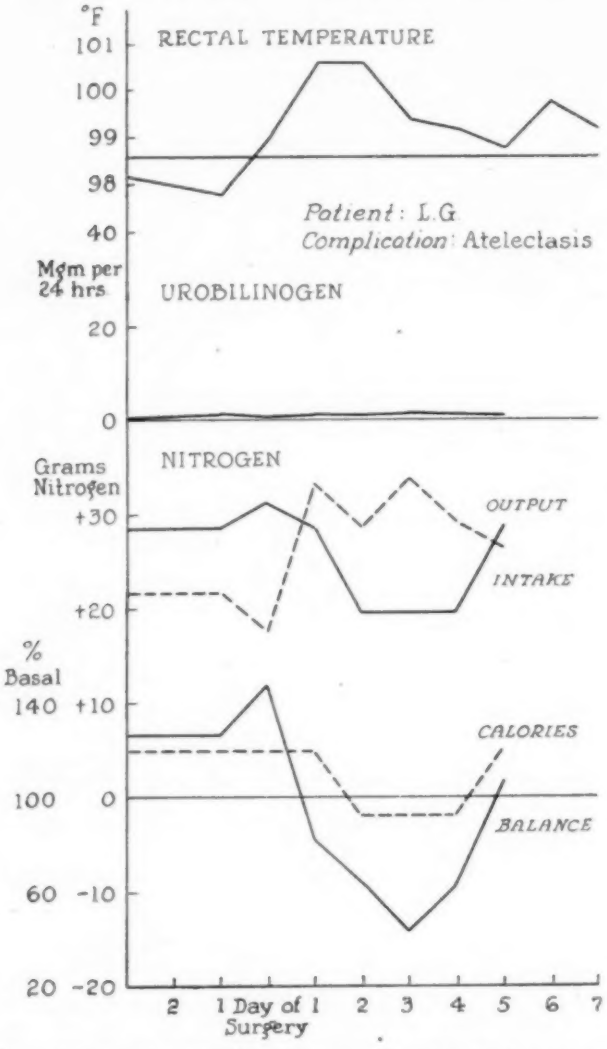

FIG. 7. The responses of a member of group XI who developed an atelectasis.

labeled with heavy nitrogen was incorporated in the serum proteins of a donor dog and its rate of disappearance from the blood of the recipient dog was noted. Within 24 hours, 50 per cent of the labeled protein had been replaced by protein containing normal lysine. With the evidence now at hand that infection also is associated with an increase in the production of cortin, the view of Albright,[7e] that the "S" hormone diverts amino acids

from protein synthesis to energy requirements, becomes quite acceptable. It furnishes a satisfactory explanation of the abeyance of protein synthesis as suggested by Peters.[9]

Alterations in Liver Function. It was planned in the present study to make, as far as possible, quantitative measurements in the alterations in liver functions, and to determine the protective value of certain therapeutic measures. The information obtained from the various tests will be used to assay the efficiency of the liver, even though there may not be an agreement as to the functions measured.

The literature covering the rôle of the liver in surgery has been recently critically reviewed by Boyce.[26] There is no need to present a general discussion of this subject.

It is well understood [27, 28] that high concentrations of a volatile anesthetic and any considerable degree of anoxia induced by the anesthetic would produce damage to the liver. The persistence of low blood pressure after a spinal anesthetic would also lead to similar anoxic states.[29] Relatively large alterations in blood flow can be induced by physiologic agents (cholinergic and adrenergic substances) in either physiologic or pharmacologic concentrations. Snyder [30] has found that with a small dose of a cholinergic agent, the outflow from the hepatic veins can be stopped, the inflow reduced, and the pH shifted during the experiment from 7.45 to 7.39. When such alterations of blood flow are ignored and the inflow is assumed to equal the output, the calculations of glucose and lactic acid added to the liver or subtracted from it varied widely (4 to 2800 per cent for glucose and 5 to 228 per cent for lactic acid). It is easily understood that these factors would produce widespread alterations in the numerous chains of chemical reactions which are a part of the normal physiology of the liver. Recovery periods would be of variable duration.

The operative load includes anesthetic effects, alteration in blood flow, the trauma of the operation, and the effects induced by the absorption of devitalized tissues. There seemed to be no simple objective method available for measuring this load. Since the anesthetics were administered by trained workers and the operations were performed by the regular surgical teams, the time consumed for the herniorrhaphy was used as an index for the operative load.

Urobilinogen Excretion in the Urine. A small amount of urobilinogen normally escapes excretion in the bile and finds its way into the urine. Even though the quantity of urobilinogen is increased in hemolytic conditions, there is no increase in the urine [31, 32] unless there is an associated failure of hepatic function. Early parenchymatous changes are revealed by an increase in the urinary urobilinogen and the quantity of urobilinogen in the urine has come to be regarded as a highly sensitive and valued index of liver function. It is therefore most important to determine the range of values for normal subjects.

Watson [33] has reported variations between 0 and 4.0 mg. per 24 hours in normal individuals. A series of normals on 84 healthy students, collected by Steigmann and Dyniewicz,[34] showed average values from 0.27 to 7.67 mg. per 24 hours. These data were made available through one of the authors (Dyniewicz) for further study. An analysis of the average preoperative urinary values in 92 of our patients showed a range of 0.53 to 9.10 mg. per 24 hours. In the series of Steigmann and Dyniewicz four subjects had an average excretion of more than 4 mg. per 24 hours. In our series there were only two patients who had an average excretion more than 4 mg. per 24 hours. In both of these series the same analyst (Dyniewicz) made all the determinations using the same method. The two groups may now be combined into a single group containing 176 normals. An analysis of the average preoperative urinary values for the combined series of patients revealed a range of 0.27 to 9.10 mg. per 24 hours with a mode of 1.24. From the tables giving areas under the normal probability curve it may be shown that 97.5 per cent of the cases will fall on or below 4.4 mg. per 24 hours. ($M + 1.96 \times$ standard deviation.)

Although our patients accepted for herniorrhaphy were in good health, as judged by the history, physical examination and other studies including bromsulfalein clearances, a few showed borderline to high preoperative values for urobilinogen excretion. In this group there were correspondingly high postoperative values. The mechanism for the excretion of urobilinogen seems to have an individually variable block, which may extend somewhat beyond the normal limits. However, any significant increase in the urinary urobilinogen is to be attributed to hepato-cellular damage,[35] which restrains the escape of urobilinogen into bile and causes it to accumulate in the blood and to appear later in the urine. For this reason it was necessary that each patient act as his own control by the calculation of an individual value for liver efficiency. The daily postoperative efficiency of the liver was expressed as a percentage obtained by dividing the average preoperative excretion by the daily postoperative excretion and multiplying by 100:

$$\frac{\text{Average preoperative excretion in mg.}}{\text{Daily postoperative excretion in mg.}} \times 100$$

Since the urobilinogen excretion approximated normal values in all groups between the fourth and sixth postoperative days an individual score for liver efficiency was calculated for the first five postoperative days. The values for the individual patients were then averaged to give a group score. High values would indicate good hepatic efficiency and low values poor efficiency.

Decrement in Liver Efficiency Measured by Urobilinogen Excretion. By reference to figures 8 and 9 and table 5, the magnitude and the duration of the decrements in liver efficiency can be noted. The excretion of urobilinogen is not strikingly increased on the day of operation but by the third postoperative day the maximal excretion is obtained.

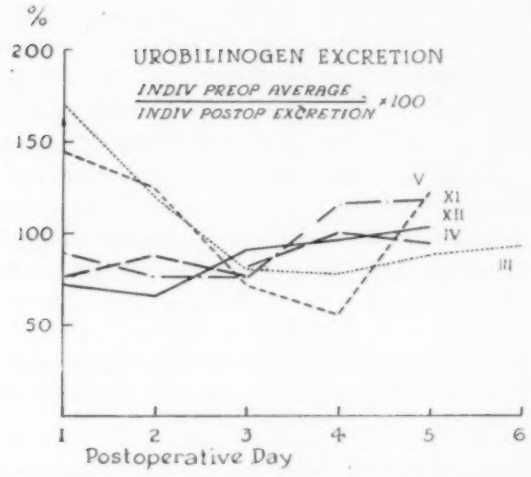

FIG. 8. The efficiency of the liver as measured by urobilinogen excretion in groups making high scores.

The groups (III, IV, V, XI, XII) which had high scores approximated their preoperative excretions on the fourth to fifth postoperative days. The groups (II, VI, VII, VIII, IX, XIII) which had lower scores did not reach their preoperative excretion levels until the sixth or later postoperative days. From the study of the managements of the groups (table 5) it will be noted that two (V and IV) who submitted to spinal anesthesia had high scores. It will be further noted that of the groups submitted to inhalation anesthesia, only three (III, XI, XII) were fed diets high in protein and these had high scores. It is therefore clear that an analysis should be run to determine the significance of these factors.

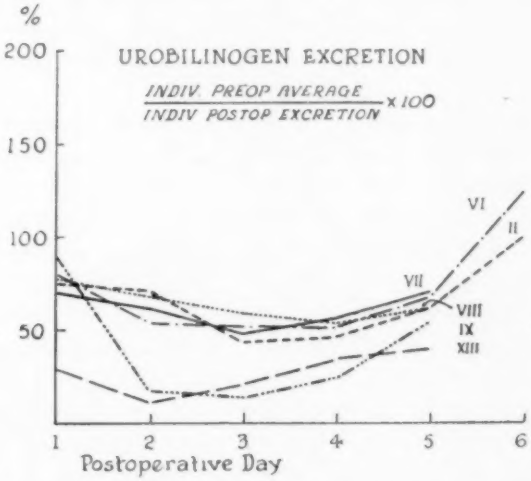

FIG. 9. The efficiency of the liver as measured by urobilinogen excretion in groups with low scores.

Groups II, IV, and V, except for the small amount of ambulation involved in the "Push-Up" test for group V, are strictly comparable and can be used to evaluate the significance of the type of anesthesia. When the 13 patients of groups IV and V were compared with the nine patients of group II they were found to have excreted significantly smaller quantities of urobilinogen ($P = 0.005$). The probability of a chance outcome is so small that it may be ignored, and it is concluded that the spinal anesthetic caused a smaller amount of liver damage as measured by urobilinogen excretion than the inhalation anesthetic. Boyce [26] using the Quick [36] hippuric

TABLE V

Postoperative Scores of Liver Efficiency Based on Urobilinogen Excretion

Group	Types of Management					Score
	Ambulation	Tube Fed	Calories	Protein	Anesthetic	
III*	+	+	Excessive	High	Inhalation	109
V	Modified	0	Submaint.	Low	Spinal	104
XI	0	+	Maintenance	High	Inhalation	96
XII	+	+	Maintenance	High	Inhalation	86
IV	0	0	Submaint.	Low	Spinal	86
VIII†	0	0	Submaint.	Low	Inhalation	64
VI	+	0	Submaint.	Low	Inhalation	61
VII	0	+	Maintenance	Average	Inhalation	61
II	0	0	Submaint.	Low	Inhalation	60
IX‡	0	0	Submaint.	Low	Inhalation	40
XIII	0	+	Excessive	Low	Inhalation	29

* Supplementation shown in table 1.
† Supplementation same as group III (table 1) plus vitamin K throughout hospital stay.
‡ Methionine 2.0 gm. daily.

acid test compared the effect of ether anesthesia with spinal anesthesia in patients submitted to elective appendectomy and herniorrhaphy. Patients submitted to spinal anesthetic showed a decreased liver function on the first postoperative day, but recovered rapidly thereafter. Those submitted to ether showed definite impairment of function of the liver through the third postoperative day and to a lesser degree through the fourteenth day.

Group XI (eight patients) with a high protein intake can now be compared to group VII (six patients) with an average protein intake. It will be noted that they both received maintenance calories and that their alimentation was maintained by tube feedings. The diet of group VII derived 15 per cent of the calories (73.4 gm.) from protein, 39 per cent (83.6 gm.) from fat, and 46 per cent (225.8 gm.) from carbohydrate. The diet of group XI derived 38.5 per cent of the calories (210.8 gm.) from protein, 22.6 per cent (54.9 gm.) from fat, and 38.9 per cent (212.9 gm.) from carbohydrate. Again there was significantly less urobilinogen excretion by the high protein group ($P = 0.013$). This indicates that a maintenance diet deriving 38.5 per cent of its calories from protein protects the liver signifi-

cantly better than a maintenance diet deriving only 15 per cent of its calories from protein. It may be argued that this beneficial effect cannot be attributed solely to the elevation of the protein (15 per cent to 38.5 per cent) since there was a simultaneous reduction in the fat from 39 per cent to 22.6 per cent. When the actual number of grams of fat (83.6) in the diet of group VII is compared to that usually taken by subjects under the dictates of the appetite, it would be moderate to low in value. It is in no sense of the word high. A value of 54.9 gm. (group XI) would be regarded as definitely low. Wilson, Pollock and Harris [43] have found no difference in the rate of recovery of patients suffering from hepatitis on diets containing respectively 202 gm. and 68 gm. of fat per day. Hoagland [42, 44] also has indicated that patients recover more readily from infectious hepatitis on diets containing 150 gm. of fat and 150 gm. of protein than on diets containing 50 gm. of fat and 150 gm. of protein. It would seem justifiable to attribute the protective value of the diet fed to group XI to the increase in protein rather than a reduction in fat. Ambulation did not alter significantly the urobilinogen excretion. In making comparisons, groups which received ambulation, and those which received no ambulation may be treated as strictly comparable. Group III may now be compared with group XIII and again the patients receiving the high protein diet (III) excreted significantly less urobilinogen ($P = 0.006$).

In a comparison of groups XI and XII with groups VI, VII, VIII and IX, the results again favor the groups with a high protein diet ($P < 0.005$). The former groups received maintenance calories and high protein; the latter received either maintenance or submaintenance calories and low protein.

Finally, when all groups (III, XI and XII) receiving high protein diets are compared with those receiving low protein diets (VI, VII, VIII and IX), disregarding the variation in the number of calories (submaintenance to maintenance) derived from carbohydrate and fat, the urobilinogen excretion is significantly lower in the high protein groups ($P < 0.005$).

When group VII (six patients) was compared with group II (nine patients) it was found that the continuous alimentation of a diet containing basal calories plus 20 per cent with 15 per cent of calories from protein was no more effective in protecting the liver than the oral ingestion of a somewhat smaller quantity of the same diet. In group XIII the calories in the diet were increased to basal plus 100 per cent using extra carbohydrate and fat, but the protein was maintained at the same level as group II. In group II the subjects ate postoperatively on successive days ¼, ½, ¾ and ¼ of their diet consisting of basal calories plus 20 per cent with 15 per cent calories from protein. When these two groups were compared it was found that the urobilinogen excretion was significantly less in group II ($P = 0.011$). The ingestion of extra calories derived from fat and carbohydrate seemed to lessen the efficiency of the liver. It is likely that the offending agent was the extra fat.

Infections and Urobilinogen Excretion. The excretion of urobilinogen of patient J. T., who developed a severe infection at the site of the repair of his hernia, is shown in figure 6. This should be compared with the urobilinogen excretion in the controls submitted to the same management, figure 5. It will be noted that the curve of excretion paralleled that of the nitrogen. The increase began at the close of the first postoperative day and returned to a normal value on the tenth postoperative day, at a time when the infection was under control. In figure 7 is found the urobilinogen excretion of L. G., who developed an atelectasis. The excretion remained within normal limits, and could be due to an absence of infection back of the obstruction. However, the nitrogen excretion rose and the nitrogen balance became negative. In the five other subjects with infection there was an increased urobilinogen excretion which returned to normal with the control of the infection.

One is impressed with the similarity in the behavior of the nitrogen and urobilinogen excretions in the presence of infection. Whether the wastage of nitrogen is to be attributed to an increased catabolism of amino acids or a failure in the synthesis of proteins, the similarity of the effects of infection on the excretion of these two constituents would indicate that the site of action is more probably on the cells of the liver than on the muscles.

Bromsulfalein Excretion. Description of test and method of scoring. Five milligrams per kilo body weight of the dye was injected intravenously. Samples of the blood were drawn at 30 and 40 minute intervals. The sum of the percentages of the dye retained at these intervals gave a numerical value for the test. All the preoperative values of dye retained by each member of a group were averaged to obtain a group value. The same procedure was followed postoperatively. Tests were run preoperatively on two days, and postoperatively on the first, third, and fifth days. A group score for the efficiency of the liver was obtained by the expression:

$$\frac{\text{Preoperative retention in per cent of dye}}{\text{Postoperative retention in per cent of dye}} \times 100.$$

This group treatment of the data was necessitated by the not infrequent preoperative zero retention of dye, despite the sampling of the blood at the 30 minute interval.

Examination of figure 10 reveals that there is an immediate drop in the score and that there is progressive recovery with a return to normal on the fifth or later postoperative day. Alterations in the diet, the addition of dietary supplements, and ambulation do not influence the function of the liver as measured by this test. Infection, on the other hand, definitely reduced the scores (table 6).

Prothrombin Percentages. Using Quick's method [37] studies in prothrombin percentages were made preoperatively and on the third and fifth postoperative days in five groups. In some groups relatively unimportant decreases were noted on the third postoperative day. Even in the group

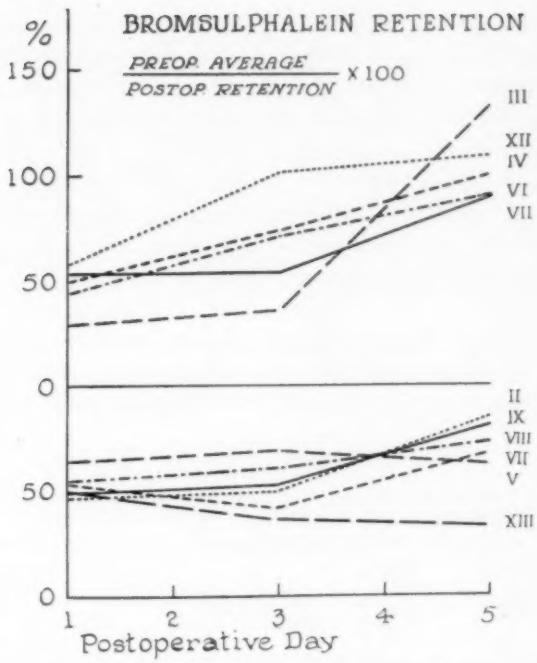

FIG. 10. The efficiency of the liver as measured by bromsulfalein retention for all groups.

TABLE VI

Bromsulfalein Retention of Patients with Complications Using Determinations on the First, Third and Fifth Postoperative Days $\frac{\text{Preoperative}}{\text{Postoperative}} \times 100$ Expressed in Terms of Per Cent of Preoperative Efficiency

Patient	Control* Complication	Score in Per Cent of Preoperative Efficiency
T	Stitch Abscess	36
	Control Group IX	61
K	Wound Infection	41†
	Control Group III	66
M	Pneumonia	31
	Control Group XI	54
L	Pneumonitis Atelectasis	23
	Control Group II	60
S	Cystitis	46
	Control Group IX	61
B	Coronary Thrombosis	38
	Control Group VIII	63

* Other members of same diet group who suffered no complications.
† Preoperative retention 0; a value of 1.0 was assumed for sake of computation.

(II) which subsisted preoperatively on maintenance to submaintenance diets and postoperatively on ¼, ½, ¾, and ¼ of this diet on successive days, there was no serious impairment of the prothrombin percentage by herniorrhaphy. However, group V which received spinal anesthesia showed a slight increase rather than a slight decrease as shown in group II. The difference between the two groups was significant ($P = 0.016$) and confirms the findings of Borgstrom [38] that patients who submitted to spinal anesthesia maintain their prothrombin indices more consistently than those who submitted to general anesthesia. It is possible that heavier operative loads might show significant impairments.

Alterations in Serum Total Cholesterol and Cholesterol Esters. In parenchymatous lesions of the liver there is some reduction in esterification of the cholesterol with a decrease in esters.[8, 39] Studies were made of the post-

TABLE VII

Effect of Operative Load in Producing Alterations in the Serum of Total Cholesterol, Cholesterol Esters, and Per Cent Cholesterol Esters

Group		Management	Preoperative Average mg./100 c.c.		Probability† Postoperative Days			
No.	No. of Subjects				3	5	7	11
Cholecystectomy								
XV	5	B+40% 15% protein ether+nitrous oxide	Total cholesterol Cholesterol esters Percentage esters	254 199 78.5	0.011 0.008 0.015	— — —	* 0.038 *	* * *
XVI	3	B+40% 15% protein spinal anesthesia	Total cholesterol Esters Percentage esters	265 212 79.3	0.004 0.009 *	* * *	* * *	* * *
Herniorrhaphy								
XIV	4	B+40% 15% protein ether+ nitrous oxide	Total cholesterol Esters Percentage esters	246 216 87.8	0.005 0.005 *	* * *	— — —	— — —

* Changes not significant.
† Refers to decrease postoperatively.

operative alterations in cholesterol and cholesterol esters in group XIV (herniorrhaphy), group XV (cholecystectomy, nitrous oxide and ether anesthesia), group XVI (cholecystectomy, spinal anesthesia). The managements of these groups otherwise were similar. It will be noted (table 7) that significant reductions were found on the third day in all three groups but a reduction of only probable significance was found on the seventh day in the esters of group XV. As measured by alteration in this function neither herniorrhaphy nor cholecystectomy appears to be a heavy load.

Alterations in Serum Total Proteins, Albumin and Globulin. Alterations in the serum proteins were studied in group XIV, group XV, and group XVI (table 8). It will be noted that in groups XV and XIV, which were submitted to nitrous oxide and ether anesthesia but different operations, there were significant changes in serum total proteins and albumin on the third postoperative day. Following the herniorrhaphy the changes had disappeared by the fifth day but they persisted after the cholecystectomy through the eleventh day. Following cholecystectomy under spinal anesthesia the changes in the albumin were suggestive but at no time definitely

TABLE VIII

Effect of Operative Load on Serum Total Proteins, Albumin and Globulin

Group No.	No. of Subjects	Management	Preoperative Average gm./100 c.c.	Probability† Postoperative Days			
				3	5	7	11
Cholecystectomy							
XV	5	B+40% 15% protein ether+ nitrous oxide	Total proteins 6.47 albumin 3.87 globulin 2.60	0.022 0.009 *	0.022 — *	* 0.004 *	0.039 0.011 *
XVI	3	B+40% 15% protein spinal anesthesia	Total proteins 6.59 albumin 4.14 globulin 2.45	* 0.045 *	* 0.045 *	* 0.015 *	* 0.041 *
Herniorrhaphy							
XIV	4	B+40% 15% protein ether+ nitrous oxide	Total proteins 6.75 albumin 4.26 globulin 2.49	0.012 0.014 *	* * *	— — —	— — —

* Changes not significant.
† Refers to decrease postoperatively.
$P < 0.030$, significant.
$P > 0.030 < 0.045$ of suggestive significance.

significant. This would indicate that the proteinogenic function of the liver is definitely impaired after cholecystectomy under nitrous oxide and ether anesthesia, but not after herniorrhaphy.

Exton-Rose Glucose Tolerance Test. The alterations in this test in patients submitted to herniorrhaphy were found to be negligible and so complete studies of all the groups were not made.

Studies were made in groups XV and XVI submitted to cholecystectomy. An analysis of the data revealed no significant differences in the behavior of these two groups when compared with each other either pre- or postoperatively.

After operation the fasting blood sugars (table 9) are significantly elevated. Since the fasting blood sugar levels were significantly altered

postoperatively the direct comparison of the pre- and postoperative 30, 60 and 120 minute values were not considered valid. Therefore the fasting values were subtracted from the subsequent values and an analysis made of the increments over the fasting levels. The probabilities on the comparisons thus made are shown in table 9. This would indicate that the ability of the liver to control blood sugar levels is altered for 10 days following cholecystectomy.

Other Liver Function Tests. Other tests of liver function were tried out in our preliminary studies and discarded as unsuitable for our purposes.

TABLE IX

Alterations in Liver Function Following Cholecystectomy Measured by Exton-Rose Glucose Tolerance Test

Time of Test	Groups	Comparison: Preoperative Value vs. Postoperative Value	
		Probability* on fourth day	Probability on tenth day
0 fasting	XV and XVI	0.010	†
30 minutes		†	†
60 minutes		0.039	<0.001
120 minutes		0.003	<0.001

* Refers to increase postoperatively.
† Change is not significant.

Simultaneous measurements were being made of physical performance and some of the patients were being submitted to ambulation. An excessive number of venipunctures interfered with these tests. For this reason intravenous glucose and galactose tolerance tests, and hippuric acid tests were discarded. The oral hippuric acid which is a valuable test interfered with our feeding schedules. The cephalin flocculation test was discarded because of variable results.

Effect of Excess Intake of Supplements and Vitamins on Efficiency of Liver. Early in our studies it seemed advisable to add to the management of one group all the factors that might conceivably facilitate convalescence. This group (III) made the highest score on the basis of all tests applied. Included in the management were the supplements described in a footnote to table 2. Again it should be emphasized that there was no reason to believe that these normal healthy subjects were deficient in vitamins. In order to analyze more specifically the effects of these supplements, they were added to the control management used for group II. Groups II, VIII, and IX are strictly comparable except as to vitamins and supplements. Group VII was also available for comparison. In this group the same diet was fed but the postoperative interruption to the alimentation was prevented by tube feeding. From table 10 it will be noted that the efficiency of the liver was the same in all of those groups as measured by urobilinogen excretion and brom-

TABLE X

Effect of Excess Intake of Vitamins and Supplements on Liver Function

Group No.	Management	Urobilinogen Score	Bromsulfalein Score	Prothrombin Score: Postoperative percentage / Preoperative percentage × 100, Postoperative Day	
				Third	Fifth
II	B+20% 15% protein	60	60	89	91
VII	B+20% 15% protein tube fed	61	66	85	100
VIII*	B+20% 15% protein supplementation	64	63	115	116
IX†	B+20% 15% protein Methionine	40	61	—	—

* Supplements described in table 1, group III, with addition of vitamin K 4 mg. daily during hospital stay.

† Methionine 2 gm. daily during hospital stay.

TABLE XI

Effect of Operative Load

Day of Operation and Five Succeeding Days, Measured by

Liver Efficiency (*a*) $\frac{\text{Preoperative Urobilinogen Excretion}}{\text{Postoperative Urobilinogen Excretion}} \times 100$

(*b*) $\frac{\text{Preoperative Bromsulfalein Retention}}{\text{Postoperative Bromsulfalein Retention}} \times 100$

Nitrogen Balance in Grams

Group		Management	Urobilinogen Score	Bromsulfalein Score	Nitrogen Balance gm. 6 days
No.	No. of Patients				
Cholecystectomy					
XV	5	B+40% 15% protein Nitrous oxide+ether	48	40	−31.1
XVI	3	B+40% 15% protein Spinal anesthesia	32	14	−29.0
Herniorrhaphy					
XIV	4	B+40% 15% protein Nitrous oxide+ether	60	47	−16.2

sulfalein clearances. In group VIII 4 mg. of vitamin K daily during the period of hospitalization was added to the supplements (group III, table 2). The questionably higher percentage of prothrombin is doubtless to be attributed to this specific factor.

Comparison of Operative Loads in Herniorrhaphy and Cholecystectomy. From tables 7, 8, 11, a comparison can be made of the operative loads of cholecystectomy and herniorrhaphy as revealed by objective tests.

There was a greater impairment in liver function tests in cholecystectomy. The urobilinogen excretion was greater, bromsulfalein clearance was somewhat more reduced, the serum proteins were altered longer, and the glucose tolerance test was altered through the tenth postoperative day.

In herniorrhaphy there was no significant alteration in the glucose tolerance test. The changes in serum proteins disappeared after the third postoperative day. The negative nitrogen balance for the day of operation and five succeeding days was greater after cholecystectomy. The clinically nonsignificant elevations in temperature associated with cholecystectomy were greater and persisted for a longer time. Boyce [26] compared 10 patients submitted to elective appendectomies and herniorrhaphies with 34 patients submitted to cholecystectomy using the hippuric acid test. There was surprisingly little difference in the behavior of the two groups after the third postoperative day. The cholecystectomy group showed a 65 per cent excretion of hippuric acid on the first postoperative day as compared with an 88 per cent excretion by the other group.

Summary

1. Data on convalescence from herniorrhaphy and cholecystectomy as it concerns nitrogen metabolism and the functions of the liver have been presented. Unless otherwise stated the conclusions apply specifically to herniorrhaphy.

2. The nitrogen excretion on the day of operation and five succeeding days was the same under an inhalation anesthetic (nitrous oxide and ether) as under a spinal anesthetic.

3. Patients who received orally postoperatively a diet containing submaintenance calories and protein showed a maximal negative nitrogen balance on the day of operation. With an increase in the diet there was a progressive return toward a positive balance by the fifth day or shortly thereafter.

4. Patients who received by tube a diet containing basal calories plus 20 per cent to basal plus 100 per cent and protein 1.2 to 2.7 gm. per kilo of body weight, retained nitrogen on the day of operation but developed a negative balance on the first or second postoperative days. The rate of return to a positive nitrogen balance was facilitated by an increase in calories derived from protein.

5. In patients who received a diet containing basal calories plus 100 per cent and low protein (0.0 : 0.3 : 0.6 : 0.9 and 1.2 gm. per kilo on succeeding

days), the negative balance was less than in the groups receiving a smaller calorie intake and the same amount of protein.

6. This wastage of nitrogen which occurred on the day of operation and the first and second postoperative days was seen in subjects to whom generous supplies of protein were given.

7. After this period of wastage has passed the patient behaves normally with respect to the conservation of nitrogen. This period may be of such short duration as to be obscured by its inclusion in a longer collection period. However the magnitude and the duration of the wastage should be a valuable index of operative trauma.

8. A positive nitrogen balance for the period covered by the day of surgery and five succeeding days was maintained by the following regimes:

(*a*) Diet containing excessive calories (B + 100 per cent) and excessive protein (2.6 gm. per kg.), administered by tube.

(*b*) Diet containing maintenance calories (B + 20 per cent) with 40 per cent calories from protein (2.7 gm. per kg.), administered by tube.

This positive balance observed in (b) was augmented by the addition of ambulation.

9. A negative nitrogen balance for the period covered by the day of surgery and five succeeding days occurred under the following regimes:

(*a*) Diets containing maintenance calories (basal + 20 per cent) and an average amount of protein (1.2 gm. per kg.), administered by tube.

(*b*) Diets containing excessive calories (B + 100 per cent) and protein at low levels (day of operation 0.0 gm., succeeding days 0.3:0.6:0.9 and 1.2 gm. per kg.), administered by tube.

Ambulation reduces but does not abolish the negative balance of patients receiving diets containing submaintenance calories and low protein.

10. Wastage of nitrogen with negative balances followed promptly the onset of infection. It is not corrected by diets containing submaintenance calories and increased quantities of protein. It is corrected by the control of the infection.

11. The efficiency of the liver was measured by the quantity of urinary urobilinogen. This proved to be a delicate index of parenchymatous liver damage. The maximal excretion occurred on the third postoperative day and the excretion returned to normal by the sixth day.

It was reduced by diets containing (*a*) excessive number of calories and 2.6 gm. of protein per kg., (*b*) maintenance calories and 2.7 gm. of protein per kg.

It was not influenced by continuous alimentation (tube) of diet containing maintenance calories and 1.2 gm. protein per kg., as compared to the discontinuous oral ingestion of reduced amounts of the same diet.

The excretion was increased in a group of patients who received by tube a diet containing excessive calories (B + 100 per cent) and low protein (0.0:0.3:0.6:0.9: 1.2 gm. per kg. on succeeding days), as compared to a group who received by discontinuous oral ingestion a diet containing submaintenance calories and the same quantities of protein. The increased excretion of urobilinogen may be attributed to a disproportion between the increased fat (130 gm.) and the low protein. The protein present may not furnish adequate number of labile methyl groups.

The excretion of urobilinogen was not influenced by ambulation.

The excretion was increased with the onset of an infection and was reduced with the control of the infection.

12. The maximal retention of bromsulfalein following herniorrhaphy occurred on the day of operation. The clearance was normal by the sixth or later postoperative days. Alterations in diet, the addition of dietary supplements, and ambulation did not influence the function of the liver as measured by the test. The effects of infection on this function of the liver were definite also.

13. Excess quantities of vitamins and other supplements, including 2 gm. of methionine daily, exerted no protective influence on liver function as measured by urobilinogen excretion and bromsulfalein clearances.

14. Herniorrhaphy produced no marked decreases in prothrombin percentages. There were significant decreases in total serum proteins and albumin on the third postoperative day which were absent on the fifth day. There were significant reductions in total cholesterol and cholesterol esters on the third postoperative day only. There were no significant changes in fasting blood sugars or in the Exton-Rose glucose tolerance test.

15. After cholecystectomy there were significant changes in the fasting blood sugars on the fourth postoperative day and in the Exton-Rose glucose tolerance test as late as the tenth postoperative day. The total cholesterol and cholesterol esters were reduced on the third postoperative day, but not thereafter. The total serum proteins were significantly reduced on the fifth postoperative day and the serum albumin as late as the eleventh postoperative day.

16. Judged by purely objective tests the operative load of cholecystectomy was definitely heavier than that of herniorrhaphy. In addition to differences enumerated under 14 and 15 the urobilinogen excretion, the bromsulfalein retention, and the negative nitrogen balance for the period, including the day of surgery and the five succeeding days, were all greater after cholecystectomy. The clinically non-significant rises in temperature were somewhat greater and persisted for a longer time.

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THE HUMAN FACTORS IN HIGH PERFORMANCE AIRCRAFT *

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About three years ago I had the honor of addressing the New Orleans regional meeting of this College on the subject of Aviation Medicine and with what now appears to be rather unbecoming smugness, I at least intimated that the physiological problems incidental to military flying were well on their way toward final solution. Events, however, have proved that such is not the case. The aircraft designers have come forth with new planes whose performances in the air present new questions in environmental physiology to which as yet we do not have the answers. These answers, however, must be provided since in high performance aircraft human factors become more and more important. As a matter of fact, aircraft designers are now giving considerable thought to the man who is to fly the plane because after all, it is the human limitation which will limit piloted aircraft performance and the closer the speed of the airplane approaches the speed of sound, the more important become these limitations of man.

To fully discuss the human factors in high performance aircraft would take more time than is allowed here and it will be possible to mention only a few of the many problems which face us, in particular those related to the design and performance of military aircraft. As an index of the multiplicity of questions which must be answered, it is of interest that the major portion of the medical research program on which the Navy has embarked deals with problems which are directly, or indirectly, related to Aviation Medicine and this research is being undertaken not only in the laboratories of the Navy, but also in the Army and in many universities throughout the country.

The first of these problems we will discuss is that of oxygen supply. At the present time the armed forces are using diluter-demand oxygen systems which automatically increase the amount of oxygen breathed as the altitude increases, but since the amount of oxygen available to a pilot depends on the partial pressure of that gas in the alveoli of the lung, there is naturally a limit to the usefulness of this particular system. Actually, at the altitude of approximately thirty-four thousand feet, at which altitude the present automatic valve supplies 100 per cent oxygen to the nose and mouth of the user, there is provided an alveolar oxygen pressure of only about 100 millimeters of mercury, because of the presence in the alveoli of water vapor and carbon dioxide. This is approximately the condition existing when breathing air at sea level. It is obvious that with this oxygen system, further ascent and further result-

* Read at the Chicago meeting of the American College of Physicians, May 2, 1947. The opinions contained in this paper are those of the author. They are not to be construed as necessarily reflecting the views or the endorsement of the Navy Department.

ing reduction in ambient pressure will cause a decrease in the partial pressure of oxygen and in the subsequent development of anoxia.

From the use of this diluter-demand system, it was a logical step to proceed with the development of pressurized systems which would supply the flier with oxygen under a positive pressure greater than that of the ambient air and thereby increasing the alveolar oxygen pressure. This development has produced satisfactory results in the design of pressurized valves and masks and has definitely increased the human ceiling by preventing the development of anoxia. However, this increase has not been proportionate to the increase in potential ceilings of new aircraft and we are still searching for further improvements which will result in preventing anoxia at high altitudes.

Another development is the introduction of pressurized cockpits. It is entirely possible to build a cockpit which could be maintained at sea level pressure when flown to any altitude. However, the loss in performance of such a craft, because of the strength and weight of the structures involved, would make its construction impracticable. The principle of the cockpit pressurization, however, has been adapted to actual use by pressurizing the cockpit to a lesser degree. Under such conditions, the pilot can reach a relatively high altitude without the use of oxygen and when oxygen is used in addition to pressurization, the pilot can reach much higher altitudes than possible with the conventional oxygen systems used in an open cockpit. Another factor which governs the degree to which cockpits can be pressurized is the possibility of explosive decompression which occurs when the cockpit is punctured, a hazard to which the military pilot would naturally be exposed. It is, therefore, necessary that a reasonable differential be maintained between the cockpit pressure and the ambient pressure in order to prevent damage to the viscera and possible fatal injury should the cockpit seal be ruptured.

There recently took place at the U. S. Naval Air Station, Pensacola, Florida, an experiment which was designated "Operation Everest." This project was designed to determine the effect of acclimatization on the development of altitude anoxia. In carrying out the project, four volunteers spent one month in a low pressure chamber during which time they were subjected to a gradual decrease of air pressure and eventually were carried to a simulated altitude of about 29,000 feet. At that altitude the subjects existed quite comfortably and performed work without the use of additional oxygen in a manner comparable to that of a non-acclimatized man at 23,000 feet. During the course of the experiment, numerous tests were performed on each of the subjects which required frequent rapid ascents on the part of the attending personnel in order to secure the respiratory, blood, and other specimens for laboratory study. Although these attendants were not exposed to low pressures for long intervals and although none were required to reach 30,000 feet, it is interesting that about one-third of these young men eventually developed symptoms of aero-embolism.

On the basis of our knowledge of aero-embolism, one would not expect those symptoms to occur at such relatively moderate altitudes and the question arises, therefore, as to the causation of unexpected aero-embolism in these cases. If the rate at which the attendants were elevated to the simulated altitude is the factor of importance, then preventive measures must be developed because modern airplanes can climb faster than these persons were elevated in the chamber. If, on the other hand, the responsibility for the development of acquired susceptibility to aero-embolism rests on rapidly repeated exposures to low pressures, then it is obvious that military missions for a combat pilot would have to be limited in number or a particular preventive device developed. At the present time, further investigation is being undertaken in an attempt to provide the answer to this interesting problem.

Another problem which is of great interest to the pilot is the question of escape from damaged high speed aircraft. The classical methods of parachute escape cannot be used in the more modern planes because of their construction and because of their performance characteristics. The danger of acute anoxia when abandoning a plane at high altitude may be largely counteracted by the use of the so-called bail out bottle which will provide sufficient oxygen for the parachute descent, but there are also to be considered the questions of wind blast and deceleration as well as the problem of clearing the tail surfaces when leaving the plane.

The answer to the last problem can be found in forcible ejection of the pilot from the airplane, and at the present time ejection seats have been developed which will throw the pilot out of the cockpit with sufficient force and speed to prevent physical injury from contact with the plane's tail assembly. During these ejections, which are accomplished by a powder blast, the pilot is subjected to acceleration up to about 16 "G." Since this is a considerable force, care must be exercised to properly position the pilot prior to ejection in order to prevent injury to the vertebrae.

In all military planes of present design, the tail surfaces, including the horizontal and vertical stabilizers, are placed above the lower surface of the fuselage and it would appear that ejection of the pilot downward instead of upward would be a more desirable method of escape. Obviously, this procedure would not subject the individual to as great a degree of acceleration as does the upward ejection since there would be no danger of contact with the tail surfaces and since the escape would be facilitated by the effect of gravity. Unfortunately, however, whatever acceleration is applied to eject the pilot downward would occur in a foot-to-head direction. We have some idea of the human tolerance to the force of acceleration when applied in the direction of head-to-foot or when applied in a direction transverse to the body, but we are not so well informed regarding tolerance when the acceleration is applied in the foot-to-head direction. We do know, however, that this position is the one in which humans are least able to withstand acceleration

and, until the investigation is completed, we are reluctant to adopt the downward means of ejection.

In addition to the danger of injury from contact with the tail surfaces, ejection from fast aircraft may take place at such speeds as to subject the pilot to the effects of excessive wind blast and to rapid deceleration. It has been stated that a wind blast of 500 miles per hour will cause severe physical injury and therefore, ejection at that, or greater, speed is not practicable. It is of interest that the original experiments on the effect of wind blast on human subjects were performed by the Germans. In this country only a small number of humans have been exposed to high velocity wind blasts in wind tunnels, but the results have definitely indicated the seriousness of the problem. It appears, therefore, that some protection to wind blast must be afforded the pilot until sufficient deceleration has taken place and the air speed reduced. In consequence, considerable thought is being given to the production of a detachable cockpit which will afford the desired protection from wind blast and from which the pilot may safely escape for a normal parachute descent after the effects of initial deceleration have sufficiently diminished.

The speed at which our modern planes will perform introduces the problem of acceleration. In this discussion, we will not consider lineal or angular accelerations but will confine our remarks to acceleration of the radial type which is produced by change in direction of motion.

If a plane, flying a straight course, is turned to the right or left, the pilot is subjected to a force acting in the opposite direction from the center of the arc of the turn. The intensity of the force depends on the speed of the aircraft and the radius of the turn. The unit used in the measurement of this force is that of the pull of gravity and hence is designated as "G."

It is, of course, obvious that both plane and pilot are subjected to the same force and that the performance of each is limited by the ability to withstand that force. The builder of an airplane, knowing the purpose for which the plane is to be used and knowing the maneuvers through which his plane is to be put, can calculate the forces which will ensue and can build his plane to withstand those forces. Unfortunately, we cannot rebuild the human body and our best efforts so far have not yet succeeded in increasing human tolerance to radial acceleration to any radical degree.

There has been developed a suit equipped with expansible bladders which inflate automatically when "G" forces are applied to the pilot and which by reinforcement of certain body areas will positively increase the human tolerance. The suit was used during the war and definitely improved the performance of fighter pilots by permitting more radical maneuvers of planes but the increased protection afforded was a matter of but approximately one and five-tenths "G." The wearing of these suits during combat or acrobatic flights also produced an unlooked for secondary result in that there was a definite diminution of fatigue. This effect was very marked and was no small factor in popularizing the suits. The cause of production of fatigue as

a result of exposure to the forces of acceleration is unknown and requires further investigation.

The last point under discussion is the question of the effect of sound waves on the human body. We are all familiar with the effect of audible sound waves on the ear and know that hearing can be reduced as the result of exposure to excessive sound intensities. However, we are not so well informed as to the effects of sound on other body structures, nor do we have knowledge of the effects of exposure to sound waves whose frequencies are below or above the audible limits. Once again the Germans were the first to appreciate the importance of investigating the physiological effects of these sound waves, probably because of their early interest in jet engines and rockets. Their work, however, was far from conclusive and was not sufficiently advanced to be of much value.

In this country investigations are underway in the field of vibration stimulated by our own use of jet engines. We have evidence to indicate that inaudible vibration waves can produce symptoms, but to date the research which has been accomplished in this field has not been sufficient to define the frequencies involved nor the physiological disturbances produced. There have been conjectures to the effect that higher frequencies, of perhaps 200,000 cycles and above, if of sufficient intensity, may interfere with reflex or voluntary actions and may even produce mental confusion. These are conjectures, however, and have not been supported by scientific experiments. Obviously, the field of investigation is a broad one and will require extensive research.

As stated before, our high performance aircraft are attaining speeds which are approaching the speed of sound. The closer such speed is neared, the more critical becomes our need to know the physiological limitations of the human pilot. The major efforts of Aviation Medicine are concentrated on that problem.

DILUTION ACIDOSIS *

By GEORGE T. SHIRES † and JAMES HOLMAN,‡ M.D., *Dallas, Texas*

IN studying the effects of rapid saline administration upon circulation and respiration in the dog, a constant and progressive acidosis of arterial blood has been noticed. This effect has been noticed by Odaiva,[1] Essen,[2] Skelton,[3] and Van Slyke,[4] but apparently this concept has not been advanced or recognized in the recent literature. Since it is a very common hospital practice for physicians to administer isotonic sodium chloride (.9 per cent NaCl) intravenously in many disease states, it was thought worthwhile to report the effect and action of this administration upon blood pH. This administration is an attempt on the part of the physician to maintain proper electrolyte, fluid, and acid-base balance, or to correct disturbances in these vital body equilibria. However, adverse effects may be obtained if saline administration is carried out during unfavorable conditions or when administered in excess.

It can be demonstrated in vitro that if one adds some neutral fluid, such as .9 per cent NaCl, to a buffer solution containing 28 millimols per liter of total bicarbonate with a 1 : 20 ratio of $H_2CO_3/NaHCO_3$, although the total buffering capacity per unit volume is lowered, the pH is not altered because the ratio of acid to salt remains constant. Assuming then that the total amount of $NaHCO_3$ in the body is approximately 28 millimols per liter—as measured by the total blood CO_2—and that there is a normal 1 : 20 relationship of $H_2CO_3/NaHCO_3$, it is readily apparent that dilution of this buffer system by some fluid such as .9 per cent NaCl would simply decrease the buffering power of the system, but as long as the 1 : 20 ratio remained constant there would be no change in pH. Since, however, there is a constant production of CO_2 by the body tissues, it is readily seen that the H_2CO_3 numerator remains constant, and it is actually the denominator which is diluted. This will change the pH of the blood buffer toward acidity, since the ratio has been seriously altered. Such a state has been termed dilution acidosis by Van Slyke.[5]

A demonstration of this effect in the intact dog has been carried out in the following manner.

(1) Dogs were anesthetized with nembutal. One femoral vein was opened for administration of .9 per cent NaCl, and one femoral artery cannulated for removal of arterial blood samples, upon which pH was determined by the Coleman pH electrometer (glass electrode method), and total CO_2 content by the method of Van Slyke and Neill.

(2) Nine-tenths per cent sodium chloride was given intravenously at

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the rate of 300 cubic centimeters per minute, with the results shown in figure 1 (a rather remarkable drop in pH from 7.55 to 7.21, the total CO_2 content of arterial blood decreasing from 49.6 volumes per cent to 31.9 volumes per cent). In all probability the flattening of the curve in figure 1 was due to a partial adjustment toward alkalinity consequent to limitation of CO_2 as a result of respiratory stimulation from (a) marked, rapid decrease in blood pH [6] and (b) increase in venous pressure as a result of increase in blood volume.[7, 8] However, this effect may have been due, in part, to the fact that

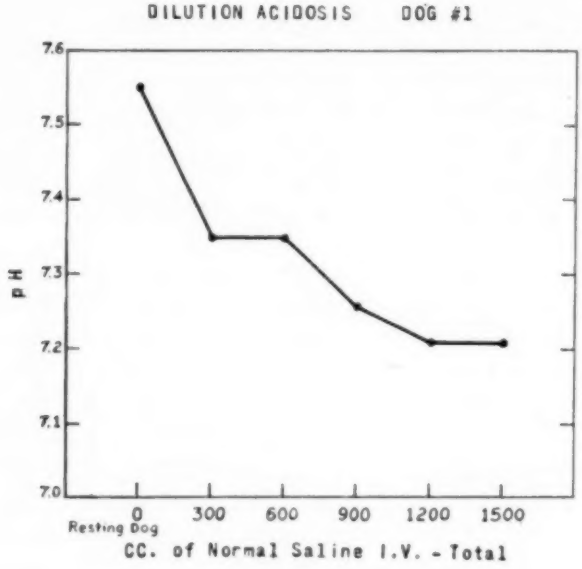

FIG. 1.

blood was diluted to its maximum extent in the first few minutes of the experiment, and the flattening represents beginning dilution of extracellular fluid in the body tissues.

As a control experiment, commercially available balanced saline-bicarbonate solution (containing 6.44 gm. NaCl, 2.52 gm. $NaHCO_3$, and .18 gm. KCl per liter which is sold commercially by the Upjohn Company under the trade name of "isonate") was administered in the same manner as described above for the dogs in which saline was used. It is readily apparent, from figure 2, that the total millimols per liter was not exactly the same in this solution (prepared for human use) as in the dogs; nevertheless, once equilibrium was reached, the same amount of fluid could be given in a similar period of time as was saline with a rise in total CO_2 content of arterial blood from 47.2 volumes per cent to 55.8 volumes per cent, without any alteration of pH.

This seems to be evidence that dilution of total body base can occur with saline administration, and that this can be prevented by giving a significant amount of $NaHCO_3$, simultaneously. Granting that this is a rather large

amount of fluid per unit of body weight and rather rapid administration, it is obvious that this principle may be of importance in fluid therapy such as:

(1) Extremely rapid administration of saline to a patient for any cause.

(2) Diabetic acidosis (remembering that in acidotic states any further decrease in alkaline reserve is likely to have adverse effects).

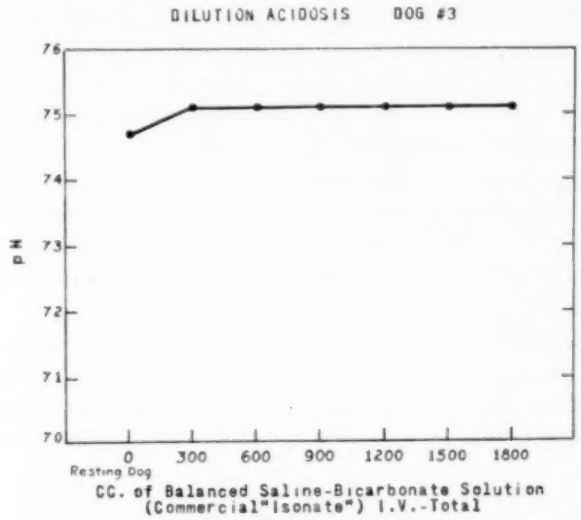

FIG. 2.

(3) Since the kidney normally will sacrifice water volume to conserve proper electrolyte concentration, any condition in which there is marked renal damage, characterized by inability to excrete electrolytes properly, will increase the tendency toward dilution acidosis. Among the conditions which may cause such a tendency are certain instances of structural damage to the kidney, and also renal circulatory disturbances from any cause.

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FUNCTIONAL PATTERNS IN RENAL DISEASE*

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The introduction of procedures by Homer Smith which permit the measurement of minimal renal blood and plasma flow, glomerular filtration rate and tubular secretory capacity has enabled measurement of renal function in terms which are functional rather than empirical. The validity of interpretations based on these methods is not seriously questioned when they are applied to the study of changes in the function of normal kidneys. Certain reservations need to be introduced in the presence of renal damage. Nevertheless, observation of changes of renal function and circulation in disease by these methods tends to reveal the nature and extent of the underlying structural changes. The patterns thus provided may support or extend a clinical diagnosis and give an objective basis for prognosis.

The purpose of this report is to review from this aspect observations made by these methods in various diseases affecting renal function. From this review of data we shall indicate the functional patterns of several forms of renal disease, and consider their relationship to concurrent structural and clinical change.

Procedures

Most of the observations were made in the ward of the Lilly Laboratory for Clinical Research, Indianapolis City Hospital. The measurements made include (1) plasma diodrast clearance at low plasma concentrations, (2) plasma inulin clearance, and (3) tubular secretory capacity for diodrast (T_{mD}). Other observations include determination of hematocrit index, plasma total protein content and arterial pressure during the test. The methods used have been described in previous reports. Some of the observations were made at the Research Division of the Cleveland Clinic Foundation. The functions measured in these instances were (1) plasma p-aminohippurate (PAH) clearance at low plasma concentrations, (2) plasma inulin clearance, and (3) tubular secretory capacity for p-aminohippurate (T_{mPAH}). In some patients of the Cleveland group, the estimate of glomerular filtration rate was made from the plasma clearance of mannitol.† To facilitate comparison of these observations with those in which diodrast and inulin were used, we have (a) estimated probable T_{mD} from measured T_{mPAH} by dividing the latter by the factor 1.8 (Chasis, Redish, Goldring, Ranges, and Smith,[1] 1945) and (b) have made allowance for the tubular

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reabsorption of mannitol (Berger, Farber and Earle,[2] 1947; Corcoran and Page,[3] 1947; Smith, H. W.,[4] 1947; and Hoobler,[5] 1947) by dividing measured plasma mannitol clearance by the factor 0.9. We have noted in the data where these factors are applied.

Plasma clearances of diodrast or of p-aminohippurate (PAH) at low plasma concentrations are accepted as equivalent to minimal renal plasma flow (RPF) from which minimal renal blood flow (RBF) is calculated using the venous hematocrit index. Plasma inulin clearance is taken as equivalent to the rate of glomerular filtration (GFR). Secretory Tm, the maximum tubular secretory capacity for either diodrast or p-aminohippurate, is a tubular function which, in most circumstances, is taken as measuring the mass of functioning tubular tissue. Reservations in interpretations of these functions in specific diseases are noted in the text. Plasma clearances, Tm_D and arterial pressure, recorded as Pm (mean of systolic and diastolic brachial pressures) constitute the *direct* observations.

The *derived* data are the clearance ratios and calculated resistances. The ratios are (a) inulin/diodrast or filtration fraction, abbreviated as FF; (b) calculated renal blood flow per unit Tm_D, abbreviated as RBF/Tm_D and (c) inulin clearance per unit Tm_D, abbreviated as GFR/Tm_D. Filtration fraction measures the proportion of water filtered per unit plasma flow. It varies with effective filtration pressure, assuming the glomeruli to be intact. RBF/Tm_D measures the rate of blood flow per unit Tm_D and, in most circumstances, is taken as indicating blood flow of functioning tissue. GFR/Tm_D measures the rate of filtration per unit secretory capacity. A change in this ratio from the normal is indicative of a change from the normal balance of glomerular and tubular functional activity.

The procedure suggested by Lamport[6] (1941) is used in calculating apparent renal vascular resistance. This method expresses as R_A (afferent resistance) the resistance to the flow of blood in the afferent tract from aorta to the end of the glomerular capillaries. R_E (efferent resistance) is the resistance from the end of the glomerular capillaries to the peritubular capillaries and is principally expressive of the resistance of the efferent arterioles. The sum of these two resistances, R is taken as measuring total renal arterial arteriolar resistance.

The text of this report is divided into eight categories of renal disease. Relevant data are provided or sources indicated. The pattern characteristic of the condition is then described with its probable mechanism. Comparison with other conditions and specific comments complete these discussions. Finally, the eight patterns are exemplified and compared, demonstrating the large degree in which they reveal underlying structural and functional disorders.

I. Hypertensive Vascular Disease (Essential Hypertension)

Our largest interest in and experience with these methods concerns their use in essential hypertension. This disease principally involves arterioles.

The renal arteriolar bed includes two sets of arterioles and since the kidneys normally receive 20 per cent of the cardiac output, it is to be expected that tests which measure hemodynamic changes will have an especial application in this disease.

(*a*) *Classification.* Essential Hypertension. This state is defined as one of persistent elevation of diastolic and systolic arterial pressures due to unknown causes and characterized by the presence of increased peripheral resistance due principally to arteriolar constriction and an increased cardiac effort.

Essential hypertension can, on clinical grounds, be variously subdivided (Page and Corcoran,[7] 1945). What seems to us a satisfactory grouping consists in viewing the process as occurring in three aspects or phases.

The first of these may be termed *early essential hypertension.* It is early in the sense that the basic process has not advanced to the point of causing or being associated with definite and serious vascular injury. It is not necessarily early in point of time, since this state may persist for several years. It is characterized by moderate, widely fluctuant, sometimes remitting increases of arterial pressures. These are associated with no more than minimal evidences of arteriovascular disease, renal or extra-renal. Most of the patients in whom the *early* phase persists for long periods show signs of disordered central nervous activity, either as the diencephalic syndrome (Page,[22] 1935) or as emotional difficulties which try the patience of their families, physicians and themselves. The coincidence in these of a lack of emotional balance with a disease process which is predominantly functional and which causes little or no progressive damage is the basis for terming the condition "neurogenic." The presumption is that the disease is based on disordered vasomotor function.

The second phase, that of *established essential hypertension,* is characterized by evidences of failure of some part of the cardiovascular system to adjust to and maintain itself against the stress of the disease. During this phase the increases of pressure are somewhat more marked than in the former groups, and less remittent. The vascular injury is slowly progressive.

The third aspect of essential hypertension is *malignant hypertension.* It is characterized clinically by evidences of rapidly progressing arterial and arteriolar damage in the form of retinopathy (papilledema, hemorrhages, and exudates). It is often associated with weight loss, hematuria, moderate proteinuria and disabilities of cardiac or cerebro-vascular origin. Such patients at autopsy reveal necrotizing arteriolitis, a more intense arteriolar sclerosis than is present in the former group. The anatomical diagnosis is usually malignant nephrosclerosis, a term which we consider inapposite since, the clinical process is often severe in extra-renal structure and may occur when renal function and structure are presumably well preserved.

The relationship of these aspects of essential hypertension to each other will be the topic of another report.

Anatomically and functionally, *arteriosclerotic hypertension* is distinct from any of the aspects of essential hypertension. However, for convenience in comparison, data from patients suffering from arteriosclerotic hypertension will be considered together with those of patients suffering from essential hypertension. Arteriosclerotic hypertension is characterized by a predominantly, often exclusively, systolic increase of arterial pressure. The condition usually has its onset at about age 50. It is only slowly progressive. A constant clinical characteristic of this condition is the tendency of arterial pressure to be widely variable and decrease to or towards normal levels during bed rest, presumably as the result of a decreased cardiac output. Functionally, the increase of systolic pressure is the result of a decreased elasticity of the aorta and greater elastic arteries.

It will be observed that the above grouping of patients is clinical. It is made without reference to data on renal function. Consequently the renal function pattern in each sub-group will reveal the correlation of quantitative changes of renal function with the clinical estimates of the nature and severity of the disease process.

(*b*) *Extra-renal Findings.* The number studied in each clinical group, the distribution by sex, mean age in years, mean estimated duration of hypertension, mean estimated severity of extra-renal vascular disease and the number of patients dying during the period of observation (mean interval three years) is shown in table 1. The estimate of duration of disease

TABLE I

Grouping of Patients Suffering from Essential Hypertension and Arteriosclerotic Hypertension

Group	Number of Patients	Male	Female	Years		Extra-Renal Disease				Died Number	Number Followed
				Duration Average	Age Average	C.	H.	E.			
Early total	32	20	12	7	32	0.2	0.1	0.6		0	32
(a) E-R-V damage present	17	12	5	6.6	29	0	0	0		0	17
(b) E-R-V damage absent	15	8	7	7.7	35	0.4	0.2	1.3		1	15
Established	76	42	34	10.7	45	1.3	1.1	2.1		23	75
								V	R		
Malignant	58	40	18	8.2	42	1.9	1.2	3.0	2.6	49	55
Arteriosclerotic	17	10	7	4.6	56	0.8	0.7	1.9	0.1	1	17

Distribution of patients with hypertension by, column (1) number examined, (2) and (3) sex, (4) average duration of disease and (5) average age. The severity of extrarenal vascular disease was estimated arbitrarily as 1 to 4+: averages for such disease in cerebral (C), heart (H) and eyegrounds (E) are shown. The latter panel is subdivided into V—representing vessels and R—representing retina, in the cases of malignant hypertension and arteriosclerotic hypertension. The period of observation averaged three years for the whole group. The number dying and number followed are indicated in columns (7) and (8). It should be added that the patient dying during observation in the early group succumbed to coronary occlusion and myocardial infarction; the one dying in the arteriosclerotic group was fatally injured in an accident. The mean duration of symptoms of malignant hypertension in this group was three months before observation.

is from the time of our observation back to the first observation of an increase of arterial pressure or to the time of the first sign or symptom of hypertensive disease. The estimates of extra-renal disease are made in three categories. These are category C, which refers to the degree of cardiac damage or strain as estimated from symptoms and from the electrocardiogram, category H, which estimates the degree of cerebrovascular disease from symptoms and signs (Taylor and Page,[8] 1945) and category E, which estimates the degree of vascular injury shown in the funduscopic examination. The latter category is subdivided, in the case of malignant hypertension, into sub categories as V (for vessels) indicating vasoconstriction and sclerosis and F (for fundus) estimating the degree of retinopathy. All estimates are made on the basis of + to ++++.

TABLE IIa

Summary: Renal Functional Data in Hypertension
(*a*) Direct Observations

Function		Normal	Early	Established	Malignant	Arteriosclerotic
R.B.F.	Mean	1075	1153	697	369	710
c.c. per	S.D.	±233	±196	±218	±228	±274
1.73 M^2	100 S.D./M.	21.6	17	31	62	39
	Range		788–1662	298–1235	75–1053	393–1042
R.P.F.	M.	674	630	393	216	407
c.c. per	S.D.	±128	±109	±115	±135	±101
1.73 M^2	100 S.D./M.	19	17	29	62	25
	Range		469–890	178–670	47–564	220–584
GFR	M.	128	130	93	61	89
c.c. per	S.D.	±20.2	+22.8	+25.3	±31.7	±29.5
1.73 M^2	100 S.D./M.	16	−17	27	52	33
	Range		77–192	44–176	15–137	47–124
Tm_D	M.	49.4	47.5	36.4	21.3	35
mg. I per	S.D.	±8.8	±5.5	±5.8	±11	±7.9
1.73 M^2	100 S.D./M.		12	16	51	22
	Range		36–62	19–55	4.5–43	21–51
Pm	M.	100	126	154	176	134
mm. Hg	S.D.		±16.2	±19	±17.8	23
	100 S.D./M.		12	12	10	17
	Range		98–165	110–200	134–213	98–180

Comments. In table 1, the group of early hypertension is subdivided according as extra-renal vascular damage is present or absent. The mean age of the patients in this group who show no evidence of extra-renal vascular damage is younger than that of patients who show some changes. However, neither this difference nor the apparent difference in duration of the disease between these two sub-groups is statistically significant (difference/standard error of the difference less than 2). Similarly, the renal functional status of the patients in the two sub-groups of *early hypertension* is identical. Consequently, this subdivision is disregarded in the discussion of renal function which follows.

The male sex is preponderant in all groups. Mean age of patients with *established essential hypertension* is 10 years greater than that of patients with *early essential hypertension.* This difference is significant (difference/standard error of the difference = 6.7). The mean age of the group with *established essential hypertension* is greater than that of the group with *malignant hypertension,* but the difference is not statistically significant. The

TABLE IIb

Summary: Renal Functional Data in Hypertension
(*b*) Derived Values

Function		Normal	Early	Established	Malignant	Arteriosclerotic
FF	Mean	0.19	0.205	0.241	0.29	0.225
	S.D.	+0.024	±0.05	±0.051	±0.04	±0.06
	100 S.D./M.	13	24	21	14	27
	Range		0.15–0.29	0.13–0.35	0.20–0.44	0.16–0.28
RBF/Tm_D	Mean	23.78	24.60	19.70	16.98	21.0
	S.D.	±3.65	±4.16	±5.61	±5.57	±4.67
	100 S.D./M.	15	17	29	33	22
	Range		17.6–34.7	13.2–32	9.46–32.8	14.9–29.2
GFR/Tm_D	Mean	2.68	2.75	2.66	2.95	2.52
	S.D.	±0.402	±0.42	±0.67	0.56	±0.38
	100 S.D./M.		15	25	19	15
	Range					
R_A	Mean	1.12	1.75	3.75	5.65	2.52
	S.D.					
	100 S.D./M.					
	Range		0.4–4.0	0.8–8.3	2.6–10.9	1.64–5.26
R_E	Mean	1.04	0.85	1.38	1.60	1.06
	S.D.					
	100 S.D./M.					
	Range		0.5–1.37	0.5–4.06	0.7–3.2	0.6–1.44
R	M.	2.16	2.85	5.11	7.16	3.54
	S.D.		±0.89	±1.81	±2.5	±1.02
	100 S.D./M.		31	35	35	29
	Range		1.55–5.98	1.37–12.4	3.36–12.6	2.4–6.56

Means, standard deviations (S.D.), coefficients of variation (100 S.D./mean) and range of observations in patients suffering from hypertension. R.B.F. = minimal renal blood flow; R.P.F. = minimal renal plasma flow; G.F.R. = glomerular filtration rate; Tm_D = maximum tubular secretory capacity for diodrast in mg. iodine; all corrected to 1.73 sq. meters body surface. Pm = average arterial pressure as mean of systolic and diastolic in mm. Hg. R_A = afferent arteriolar resistance, R_E = efferent resistance and R = total resistance ($R_A + R_E$) in mm. Hg per c.c. of blood flow per unit Tm_D. These symbols have the same significance in subsequent tables.

group with *arteriosclerotic hypertension* is significantly older than the *established essential* group.

From the estimate of duration, the onset of disease in the *early* group would occur at mean age 25 and in the patients with *established essential hypertension* at mean age 34. This difference and the similar difference when the comparison is made with the patients who suffer from *malignant hypertension* are probably artefacts which reflect the greater frequency of

observations of arterial pressure in recent years. If this explanation is granted, it seems likely that the brief duration of hypertension in the *arteriosclerotic* group is accurately estimated.

(*c*) *Renal Function.* The observations with which the data are composed were made at the time the patient first came under observation. Because of the large number of observations, the data are presented as a statistical summary. Observations made during some reversible states such as cardiac failure are excluded. Means, standard deviation [S.D. = $\sqrt{\Sigma}/(n-1)$] coefficients of variability (100 S.D./mean) and the range of variation are listed. The direct observations from plasma clearances and arterial pressure are presented in table 2a. Values derived from these (derived data) are collected in table 2b. In both tables the comparison is made by clinical groups with data from normal subjects.

Early Essential Hypertension. Means of direct observations with the exception of arterial pressure are well within the range of data from normal

TABLE III

Renal Function in Cushing's Syndrome

No.	RBF	RPF	GFR	Tm_D mg.	Pm	FF	RBF/Tm_D	GFR/Tm_D	R_A	R_E	R
	c.c. per 1.73 sq. m./min.						c.c./min.				
1	687	374	77	39.9	—	0.21	17.2	1.92	—	—	—
2	495	271	77+	32.2+	135	0.28	15.4	2.38	3.78	1.42	5.20
3	518	295	71	27.8+	120	0.24	18.6	2.54	2.05	1.24	3.33
4	446	201	71+	26.7+	140	0.35	16.7	2.66	2.82	1.95	4.77
5	463	278	59+	19.6+	122	0.21	23.6	3.0	2.48	0.64	3.12

subjects. Among the derived data (table 3) only R_A and R are increased. In this condition, then, there is usually normal renal blood flow, glomerular filtration rate and tubular secretory activity, but an increase in vascular resistance in the afferent tract which accounts for an increase in renal resistance. Variability of FF is greater than in normal subjects.

Established Essential Hypertension. Mean values of the direct observations are definitely abnormal (table 2a). The ratios to the normal of the means are as follows: RBF = 0.65, RPF = 0.58, GFR = 0.73, Tm_D = 0.73, Pm (mean of systolic and diastolic brachial arterial pressures) = 1.5. Means of derived values other than GFR/Tm_D are similarly abnormal. The ratios of these to the normal are FF = 1.27, RBF/Tm_D = 0.83, GFR/Tm_D = 0.99, R_A = 3.3, R_E = 1.3, R = 2.3. Many values observed in patients of this group extend into the range observed in patients with *early essential hypertension* and in normal subjects. However, the average pattern is one of loss of tubular secretory capacity, a more extensive depression of blood and plasma flow, a less severe decrease of glomerular filtration, and increase of FF. The increased resistances, both afferent and efferent, lead to reduction of renal blood flow to the residue of tubular tissue.

Malignant Hypertension. Means of direct observations are still more abnormal than in the last group. The ratios of change from the normal are as follows: RBF = 0.34, RPF = 0.32, GFR = 0.48, Tm_D = 0.43, Pm = 1.7. Means of derived values other than GFR/Tm_D are grossly abnormal, their ratios to normal being FF = 1.5, RBF/Tm_D = 0.7, GFR/Tm_D = 1.1, R_A = 5.1, R_E = 1.5 and R = 3.3. Even in this phase a few patients yield some values which are not significantly abnormal. But the mean pattern is an exaggeration of the changes seen in the preceding group.

Comment

Early Essential Hypertension. The normal values for all functions other than renal resistance demonstrate that renal ischemia is not the cause of hypertension in this phase and indicate that the initial renal vascular change is constriction of afferent arterioles. Comparison of the renal functional states of such patients with those in other groups indicate the renal parenchymal damage in the other groups is a sequel to rather than a cause of essential hypertension. It should be noted that the absence of renal functional abnormality in these tests is not evidence of an extra-renal origin of the hypertensive disease, since experimental renal hypertension can be produced in dogs without demonstrable or lasting impairment of excretory function (Corcoran and Page,[9] 1942).

The 33 per cent increase in renal resistance present in these patients affects 20 per cent of the cardiac output. The concurrent increase in total peripheral resistance may be estimated at 25 per cent. The renal arteriolar constriction present in these patients therefore accounts for 30 per cent of the increase in total peripheral resistance.

Finally, variability of some functions in this group as contrasted with normal subjects testifies to the occurrence in the renal vascular bed of the vasomotor instability so characteristic of early essential hypertension.

Established Essential Hypertension. The reduction of blood flow, filtration and tubular secretory capacity indicates a loss of tissue or at least a suspension of function. Assuming, as seems likely, that the decrease in Tm_D is due largely to loss of nephrons, this loss is found to average 27 per cent. It is associated with a proportionate decrease in glomerular filtration rate. The reduction in these functions is presumably due to arteriolarsclerotic obliteration with focal ischemic atrophy. The mean reduction in minimal renal blood flow is greater proportionately than the changes in Tm_D and filtration. The secreting tissue which remains in function is therefore ischemic, since it is receiving on the average only 83 per cent of its normal quota of blood. Since glomerular filtrate is squeezed from the plasma by hydrostatic pressure, it follows also that glomerular filtration pressure is increased. These changes are associated with increases in renal resistances, afferent and efferent. The increase in efferent resistance is probably due to vasoconstriction, since this arteriole is rarely sclerotic. The increase in

afferent resistance is attributed to the summation of afferent arteriolar constriction with arteriolar sclerosis.

Alternative explanations of some of these changes have been proposed (Smith,[10] 1941; Goldring and Chasis[11]; Findley, Edwards, Clinton and White,[12] 1942). In these it is assumed that the kidney in hypertension suffers specific injuries which alter the normal interpretation of changes in the clearance pattern. Evidences of such injury have been demonstrated in some patients (Smith,[13] 1943). However, since the interpretation proposed here is consistent with what is known of the anatomical and functional changes present in *established essential* hypertension, we believe that it will apply to most patients.

The contribution of renal vascular resistance in functioning areas to total peripheral resistance in this phase of the disease can be estimated as 20 per cent.

Malignant Hypertension. In this stage there is on the average nearly twice as much loss of Tm_D, presumably due to loss of tubular tissue, as was present in *established essential hypertension.* The tissue remaining in function receives only 70 per cent of its normal blood flow. Renal vascular resistance is increased to a greater degree than in the former group. The increase of resistance and greater loss of tissue testify to the greater severity of renal vascular injury, both constrictive and sclerotic, present in malignant hypertension as compared with established essential hypertension.

The values in some patients extend into the normal range, but in most these values, which are our first observations in these patients, testify to a process which is already far advanced. The skewed scatter of data testifies to the rapidity of renal functional deterioration. Most of these patients are first seen only when renal damage is severe.

Arteriosclerotic Hypertension. The pattern resembles in most respects that seen in *established essential hypertension.* The difference consists in the fact that the increase in vascular resistance in functioning areas is predominantly afferent. The coincidence of afferent resistance with tissue loss speaks for an obstructive rather than vasoconstrictive lesion and accords with the structural and functional changes underlying *arteriosclerotic hypertension.* Functional data do not indicate the focus of the obliterative afferent renal vascular lesions. Anatomical data show that it affects larger arterial channels, rather than the arterioles which are affected in essential hypertension.

Summary. The renal functional pattern in *early essential hypertension* is that of a condition which is functional, in which there is neither renal ischemia nor loss of nephrons and in which vasoconstriction extends only to the afferent arteriole. In the phase of *established essential hypertension,* arteriolar sclerosis is present with consequent renal structural loss. There is vasoconstriction of afferent and efferent arterioles, and, usually, some ischemia of the tubular areas remaining in function. Glomerular filtration pressure is increased. In *malignant hypertension* the changes present in

the established essential phase are greatly exaggerated. The average pattern is one of severe structural loss with severe arteriolar sclerosis and constriction of arterioles, ischemia of the tissue remaining in function and a marked increase in glomerular filtration pressure. Since some of the observations extend into the normal range and many into the range observed in the phase of established essential hypertension, it is evident that the syndrome of malignant hypertension is not the result of renal excretory insufficiency. Rather, the spread of the data indicates that it is a process which is characterized by a rapidly progressive renal vascular damage. *Arteriosclerotic hypertension* reveals a pattern consistent with obliterative lesions of afferent arteries or arterioles which does not usually result in a severe loss of renal function and in which vasoconstriction is presumably absent. The demonstration that similar renal functional patterns occur in old age in the absence of hypertension (Shock,[23] 1946) does not militate against this interpretation.

Most of these conclusions find support in the data of former writers (Chesley and Chesley,[14] 1940; Friedman, Selzer and Rosenblum,[15] 1941; Foa, Woods and Peet,[16] 1942; Steinitz,[17] 1941; Talbott, Castleman, Smithwick, Melville and Pecora,[18] 1943; and Hilden,[19] 1946; and others).

II. Other Disorders Associated with Arterial Hypertension

(*a*) *Cushing's Syndrome.* Observations were made in one male and three female adults referred by Dr. E. P. McCullagh. These presented the typical clinical pattern of Cushing's syndrome. All showed systolic and diastolic arterial hypertension, and their retinal arterioles revealed constriction and sclerosis.

The results of tests of renal function are shown in table 3 in which is included an observation made by Barnett, Perley and Heinbecker[20] (1943) in an adult suffering from this condition (No. 1). The renal functional pattern is similar to that of established essential hypertension. In our four patients the levels of RBF are relatively uniform and lie well below the mean found in our group of *established essential hypertension,* as does also the mean of Tm_D. In the observation cited from Barnett, Perley and Heinbecker, the levels of function are higher. The pattern in our patients is one which testifies to loss of renal tissue as the result of obliterative arterial and arteriolar disease, associated with constriction of the afferent and efferent arterioles in functioning areas.

It is tempting to attribute the renal vascular lesion in this condition to nephrosclerosis resulting from excess of cortical steroids, to draw an analogy of the lesion produced in animals by administration of large doses of desoxycorticosterone (Selye,[21] 1946) and to consider the arterial hypertension as due to stimulation of renal pressor activity consequent on nephrosclerosis. That this is the mechanism of the renal injury and the hypertensive disease in Cushing's syndrome is far from established. But, assuming the analogy to be exact, restriction of sodium and administration of ammonium salts is

indicated as a means of retarding the progress of the lesion. The comparatively low levels of renal function found in our patients with Cushing's syndrome testifies to the importance of the renal lesion in this condition and the desirability of controlling its spread.

(*b*) *Pyelonephritis* (table 4). Observations were made in five patients in whom chronic pyelonephritis was associated with arterial hypertension and in two patients whose levels of renal function lie in the same range, but in whom arterial pressure was normal. The renal lesion was not *acutely active* in any one of these patients at the time of observation. For the sake of

TABLE IV

Renal Function during Chronic Pyelonephritis

No.	RBF	RPF	GFR	Tm_D	Pm	FF	RBF/Tm_D	GFR/Tm_D	R_A	R_B	R
	c.c. per 1.73 sq. m./min. mg.						c.c./min.				
(1) With Arterial Hypertension											
6–10 (av.)	689	409	96	38.2	160	0.23	18.0	2.50	4.56	1.24	5.80
(2) Normotensive Inactive											
11–12 (av.)	413	249	50	22.5	107	0.20	184	2.20	1.16	1.11	2.27
(3) Active											
13	433	316	39.5	12.8+	100	0.12	33.6	3.09	—	—	—
14	409	262	29.3	11.3+	136	0.11	36.2	2.60	—	—	—

comparison, then, we have included in table 5b observations made in two patients suffering from chronic pyelonephritis in whom the process was active (as evidenced by fever, leukocytosis, pyuria, tenderness over the renal areas) at the time of observation.

The functional pattern in the patients in whom pyelonephritis is associated with hypertension is nearly identical with that present in established essential hypertension. The pattern in the two normotensive patients in remission is one of simple loss of function. In the patients in whom the renal inflammatory reaction was *acutely active* at the time of observation, the levels of filtration rate and fraction are greatly reduced and RBF/Tm_D increased. The changes in other functions are consistent with simple loss of tissue.

The functions of tubular secretory capacity, renal blood flow and glomerular filtration rate were decreased in all the observations. The loss of tissue in the normotensive patients must be taken as a result of the inflammatory process. It is therefore likely that inflammatory injury as well as arteriovascular disease participated in reducing function in the groups in

whom hypertension is present. In contrast to the findings in the normotensive patients in whom the disease is inactive, the decrease of filtration rate and fraction in the patient with an active lesion suggest that there is a decrease in effective filtration pressure. A decrease in filtration pressure might result from increased renal interstitial pressure consequent on the inflammatory reaction. However, the increase in RBF/Tm_D during the active phase suggests that there is a loss of tubular secretory capacity which is out of proportion to the level of RFF and presumably CFR. This abnormality is seen also in diffuse glomerulonephritis (see below).

TABLE V

(*a*) Acute Diffuse Glomerulonephritis

No.	RBF	RPF	GFR	Tm_D	Pm	FF	RBF/Tm_D	R_A	R_E	R	GFR/Tm_D	T.P.
1	1544	857	110	64	100	0.13	24.3	1.25	0.65	1.90	1.72	6.9
2	1478	872	103	36	95	0.12	41.2				2.93	8.2
3	1328	784	123	43	87	0.16	30.9	0.65	0.48	1.13	3.1	6.1
4	1192	668	69	26	95	0.10	46.0	0.78	0.26	1.04	2.7	5.5
5	765	507	49	39	95	0.10	19.4	1.25	0.72	1.97	1.26	6.9
6	652	437	59	25	110	0.14	26.0	1.87	0.52	2.4	2.35	6.6
7	413	272	22	91	120	0.08	45.0	1.38	0.25	1.6	2.4	6.1
8	263	173	17	4.0+	105	0.10	66.0	0.84	0.08	0.96	4.25	5.5
9	235	143	21+	4.2+	133	0.15	56.0	1.30	0.24	1.54	4.85	5.0
					Healing Stage							
3	1065	628	113	48	92	0.18	22.2	1.10	0.72	1.85	2.35	6.1
5	1007	689	124	55	91	0.18	18.3	1.15	0.90	2.05	2.25	7.0
6	722	419	85	33	112	0.20	22	1.42	0.97	2.37	2.57	7.6
7	718	424	92	365	80	0.22	19.7	0.52	0.89	1.41	2.51	5.9

(*b*) Chronic Diffuse Glomerulonephritis (Pre-Terminal)

No.	RBF	RPF	GFR	Tm_D	Pm	FF	RBF/Tm_D	R_A	R_E	R	GFR/Tm_D	T.P.
9	1526	938	110	62	116	0.12	24.5	2.5	0.46	2.95	1.78	4.5
10	1172	647	106	43	107	0.16	27.3	1.8	0.47	2.25	2.47	4.6
11	1094	613	83	42+	110	0.14	26.0				1.98	4.2
12	1056	644	116	46	100	0.18	23.0	1.84	0.57	2.41	2.52	5.0
13	980	441	42+	20.4+	114	0.09	48.0				2.06	4.6
14	966	512	85	37	140	0.17	26.1	3.08	0.51	3.59	2.30	5.2
15	951	514	110	36	123	0.21	26.4				3.05	6.6
16	689	658	60	35	129	0.09	25.4	2.89	0.43	3.32	1.72	4.1
17	670	456	70	21	125	0.15	32.0	2.23	0.76	2.99	3.3	4.4
18	589	298	60	28	129	0.20	21.0	2.12	1.06	3.18	2.2	5.9
19	541	360	61	27	110	0.17	20.0	1.87	0.85	2.72	2.2	6.2
20	476	314	42	16	147	0.14	29.7	2.90	0.44	3.34	2.7	5.4
21	256	167	53	26	127	0.32	9.9	5.81	1.96	7.77	2.0	5.1

(*c*) Terminal Phase (Mean of Observations in 11 Patients)

22–33 (av.)	80	57	10	2.3	135	0.17	34.3	—	—	—	4.35	6.2
range	138–40	97–32	19–3	8.0–0.3	123–157	0.17–0.28	—				—	—

(T.P. = plasma total protein gm./100 c.c.)

From the aspect both of renal functional pattern and clinical impression, the hypertensive disease in the patients in whom hypertension and pyelonephritis are associated is identical with that of well established essential hypertension. The chronic inflammatory renal lesion seems to act as an intra-renal fibrosing equivalent of the extra-renal collagenous reaction of experimental hypertension due to perinephritis (Page,[24] 1939). A significant difference lies in the mean age of these five patients, which was 23 years. The presence of established hypertensive disease at an early age may be a clue to the discovery of its source in pyelonephritis.

(*c*) *Diffuse Glomerulonephritis.* The degree of renal injury in the acute and chronic stages of diffuse glomerulonephritis is so widely variable that an average of observations made in either of these groups can have little meaning or value. The observations in individual patients are presented in table 5. A mean is taken in the 11 patients observed in the terminal stage of chronic glomerulonephritis, when the levels of function are low and comparatively uniform.

Acute Diffuse Glomerulonephritis. The observations in nine patients are listed in table 6a. In these, RBF varies from 1.43 to 0.22 times mean normal; GFR varies from 0.8 to 0.13 times other mean normal and Tm_D from 1.27 to 0.08 times mean normal. While direct observations of renal function thus show a wide variation from values which exceed mean normal to low values, glomerular filtration is subnormal in every instance. This

TABLE VI

(*a*) Intercapillary Glomerulosclerosis

No.	RBF	RPF	GFR	Tm_D	Pm	FF	RPF/Tm_D	R_A	R_E	R	GFR/Tm_D	T.P.
34	1077	657	61	58+	91	0.09	18.6	1.76	0.63	2.4	1.05	5.0
35	946	596	82	26+	135	0.14	36	2.23	0.34	2.6	3.12	4.2
36	609	414	59	21+	130	0.14	29	2.29	0.47	2.76	2.8	5.6
37	477	339	28	18	146	0.08	26	3.2	0.46	3.65	1.56	5.7
38	222	139	25	11+	123	0.18	20	2.77	0.79	3.56	2.28	5.9
39			13	2.7	141						4.8	6.4
(*b*) Toxic Nephrosis (Vitamin D Intoxication)												
40	286	192	37+	10+	137	0.19	28.6	—	—	—	3.7	7.0
41	407	285	48+	12.6+	88	0.17	32.4	—	—	—	3.8	6.0
41 repeat	592	361	93	37	88	0.26	16.0					
(*c*) Hypotension Due to As_2O_3												
42	670	415	34	47	48	0.08	14	—	—	—	0.7	4.7
Orthostatic Hypotension												
43a	376	240	54	18.5	124/85	0.22	20.3				2.82	6
43b	131	87	20	(18.5)	75/62	0.23	7.1				1.07	

depression of glomerular filtration relative to concurrent changes in blood and plasma flow is shown in levels of filtration fraction. This function is depressed in every instance. The average for the group is 0.12.

The increase in the ratio RBF/Tm_D in seven of nine observations is indicative either of hyperemia in the tissue which remains in function or of a reduction in tubular secretory capacity. The depression of Tm_D was observed in eight of the nine patients. In these, Tm_D was either subnormal at the time of the observation, or, if still within the range of normal, was found to increase on healing in the four patients observed in this stage. Thus, depression of Tm_D is at least a partial explanation of the increase in the function RBF/Tm_D. That there may be associated with this a true renal hyperemia in acute glomerulonephritis is suggested by the demonstration of an increase in total renal blood flow at the onset of experimental glomerulonephritis in dogs (Fouts, Corcoran and Page,[52] 1941). Similar renal changes have been shown by Hilden [25] (1943) and by Earle, Taggart and Shannon [26] (1944).

Thus the apparent renal hyperemia of the residue of functioning renal tissue commonly present in acute glomerulonephritis is probably partly real and partly apparent. The apparent hyperemia (apparent increase in renal blood flow per unit of residual tubular secretory capacity) is termed by Smith [13] (1943) "vicarious hyperemia," although it seems to us (Corcoran, Taylor and Page,[27] 1943) more appropriately termed a "vicarious clearance." It is attributed to secretion by active tubules of material which is not conveyed to them in their own peritubular capillaries but which is diffused in the interstitial fluid from blood which is circulating around inactive tubules. The clearance is vicarious in the sense that the blood is cleared of diodrast or p-amino-hippurate by cells with which it is not in close contact. This vicarious clearance probably accounts for some of the decrease in filtration fraction since it yields a level of apparent effective renal plasma flow which is greater than the volume of plasma perfusing functioning tubules.

The pattern of renal functional change in acute diffuse glomerulonephritis is seen as one which is widely variable, according to the severity of the lesion. In some patients most of the nephrons seem to be in active, if abnormal, function, while in others function is almost suppressed. The characteristic abnormality is a depression of glomerular filtration, measured either as a decrease in glomerular filtration rate, or more consistently, as a decrease in filtration fraction. With this is commonly associated an increase in the derived value RBF/Tm_D due to both hyperemia and to depression of Tm_D.

The decrease of filtration reflects the specific lesion of this disease, which is glomerular. The character of the renal change suggests that parts of the glomerular capillaries involved by the lesion become impermeable as filters, though their lumens may still be patent and permit the flow of blood. The presence of a predominantly glomerular lesion is confirmed in two of the patients by depression of the ratio GFR/Tm_D. The frequent decrease of Tm_D in this condition reflects loss of tubular secretory capacity due to one of

several causes. Among these, probably the most important is obstruction of glomerular capillaries with consequent suppression of excretory function in the nephrons. Another cause is obstruction of renal tubules by protein coagula (Oliver,[28] 1940; Blackman, Goodman and Buell,[29] 1941). It is also possible that the degenerative changes of tubule cells attributed to retention of protein reabsorbed from the protein-rich tubular fluid (Dock,[30] 1942) plays a part in inhibiting tubular secretion of diodrast. The increase in the function RBF/Tm_D is taken partly as a reflection of true renal hyperemia and partly as evidence of vicarious clearance of diodrast.

The Stage of Healing. Observations were made in four of the eight patients during the stage of healing. The pattern in two of the four patients is one of complete restoration to normal. In the other two patients the absolute level of function remains subnormal, although the derived values (FF, RBF/Tm_D) are normal, which suggests complete subsidence of an inflammatory reaction which, however, has been so severe that considerable portions of the kidneys are completely functionless.

Chronic Diffuse Glomerulonephritis (table 5b). Observations were made in 13 patients who were seen before they had reached the terminal phase of the disease (table 5c). As in the acute phase, the absolute levels of function are widely variable. It is somewhat surprising to find that both RBF and Tm_D were greater than mean normal in one patient and within the normal range in eight. Filtration fraction was reduced below normal in nine patients. The average level of this function is higher than in the acute phase. The ratio RBF/Tm_D is greater than mean normal in eight instances. The ratio GFR/Tm_D is decreased in seven of the patients. This change is taken as evidence of a predominantly glomerular defect. Hypoproteinemia is present in every instance. The renal functional pattern of one patient (no. 21) resembles that of malignant hypertension, as, at the time of observation, did the clinical syndrome.

Thus, the renal functional pattern in chronic diffuse glomerulonephritis is similar to that of the acute phase. It differs in that filtration fraction is more often within the limits of normal, in the uniform presence of hypoproteinemia, and in the appearance of a clinical and renal pattern similar to that of malignant hypertension in one patient. The parallelism of the functional pattern with that of acute glomerulonephritis indicates the similarity of structural changes present in the two phases of this disease. Depression of filtration reflects the glomerular lesion. Depression of Tm_D is due to the causes considered in discussing the acute phase. The increase in RBF/Tm_D in the chronic phase is probably wholly the result of vicarious clearance rather than of hyperemia. This is suggested (a) by the absence of absolute renal hyperemia in the chronic state of experimental glomerulonephritis and (b) the absence of structural evidences of hyperemia in sections from kidneys of patients suffering from chronic glomerulonephritis.

Terminal Chronic Glomerulonephritis (table 5c). The abnormalities of renal function present in this stage, their relation to the concurrent structural

changes and value in diagnosis and prognosis have been considered previously (Corcoran and Page [31] (1944)). The outstanding features in this phase are (a) the extremely low levels of Tm_D, (b) the comparatively low levels of RBF and GFR which are consistent with survival for periods of months and (c) the phenomenon of focal saturation.

The disproportionate reduction of Tm_D as compared with other functions supports the view that the apparent renal hyperemia (increase in RBF/Tm_D) observed in the chronic pre-terminal and acute phases of the disease are partly or wholly the result of vicarious clearance. A consequence of this severe loss of tubular secretory capacity is the appearance of focal saturation, i.e., of a state in which varying severity of the lesion in different nephrons results in some being saturated by the secretable substance (diodrast or p-amino-hippurate) at very low plasma concentrations while others are not. The presence of this is suggested by finding high levels of filtration fraction in a disease process in which it is probable that filtration is as much or more depressed than blood flow. The findings confirmed by titration of tubular secretion at varying plasma levels. The plasma clearance of diodrast obtained in this condition does not reflect effective renal plasma flow. Consequently the means of RBF, RPF and RR listed in table 6c do not include the six observations in which this phenomenon was present during the measurement of plasma clearance.

Summary

Glomerulonephritis. The renal functional changes as observed in patients suffering from diffuse glomerulonephritis have been reviewed and the underlying mechanisms discussed by Earle, Taggart and Shannon [26] (1944). The patterns which they describe in the various phases of the disease are similar to those we present. The distortion of the pattern from the normal in the various stages of the disease are those which might be predicted from a knowledge of the concurrent structural changes, with the exception perhaps of the severe loss of tubular secretory capacity present in severe acute glomerulonephritis.

The differences in renal patterns between terminal glomerulonephritis and malignant hypertension with early renal failure have been reviewed previously, the most important points being the tendency in terminal glomerulonephritis to reduction of Tm_D below 5 mg. per minute and of GFR below 10 c.c. per minute. In the other stages of the disease the differences between glomerulonephritis and hypertensive disease lie (1) in the presence in glomerulonephritis of a decrease in FF which persists at least until the disease is far advanced, (2) in the frequency with which the ratio RBF/Tm_D is increased in glomerulonephritis, whereas it is decreased in the course of essential hypertension and (3) in the occurrence of a depression of the function GFR/Tm_D in 9 of the 22 patients.

Since chronic glomerulonephritis at times causes a clinical syndrome indistinguishable from that of malignant hypertension, it is of interest that in

one such patient the renal functional pattern is that of malignant hypertension rather than that of the underlying but overshadowed glomerulonephritis.

(*d*) *Intercapillary Glomerulosclerosis.* Observations were made in six patients, four of whom were referred by Dr. E. P. McCullagh, suffering from intercapillary glomerulosclerosis (Kimmelstiehl-Wilson syndrome). These are listed in table 6a whence they may be compared with the pattern in glomerulonephritis.

The range of variation, like that of chronic glomerulonephritis, is very wide. The patterns are otherwise similar, with reduction in GFR, Tm_D, FF, an increase of the ratio RBF/Tm_D and in three patients a decrease of the ratio GFR/Tm_D. As in chronic glomerulonephritis, there is no reason to ascribe the increase of the ratio RBF/Tm_D to actual hyperemia of the residue of functioning tissue. Consequently, we attribute it to vicarious clearance. As in terminal glomerulonephritis, focal saturation and a very low level of Tm_D are found in the terminal stage of the disease.

The mechanism of the change is similar to that of glomerulonephritis. The pattern is one of decreased filtration, presumably due to lesions of the glomerular capillaries which render many of them impermeable to filtrate, although still perfused by blood. With this is associated a loss of tubular secretory function due to actual loss of whole nephrons by (1) glomerular and (2) tubular occlusions and (3) to interference with the tubular functions of those which remain in partial function.

(*e*) *Toxemia of Pregnancy.* The renal functional pattern of the specific eclamptogenic toxemia of pregnancy is similar to that of acute glomerulonephritis (Corcoran and Page, 1941,[32] 1942 [33]). The range of RBF varies from supernormal to subnormal levels. GFR and FF are depressed. Tm_D tends to vary with the level of RBF. The pattern is one of interference with filtration. This has been attributed to constriction of afferent arterioles. We prefer to regard it as an expression of the glomerular lesion present in this condition (Bell,[34] 1945) in which increased renal interstitial pressure may also participate.

Delivery is followed by relief of toxemia and, in most cases, by complete restoration to normal of functional levels. A few post-toxemia patients show a persistent decrease of FF which is presumed to be a reflection of the persistent glomerular lesions found in post-toxemic women by Page and Cox [35] (1938). Others develop the clinical and renal functional manifestations of essential hypertension. In some of these the level of FF is frequently normal, i.e., less than would be predicted from clinical and renal functional state in a condition resembling established essential hypertension (Chesley,[36] 1941). This, like the low level of FF found in some post-toxemic normotensive women may reflect persisting healed glomerular damage. Since the renal and clinical functional pattern of essential hypertension may follow a toxemic pregnancy which was not preceded by hypertension, it seems likely that the hypertensive disease originates in the renal injury sustained during the toxemia.

The renal functional pattern of patients with essential hypertension persists unchanged during and after pregnancy except as it may be modified by the superimposition of specific toxemia of pregnancy. Observations similar to these have been made by Taylor, Wellen and Welsh [38] (1942), Chesley [36] (1941) and Dill, Isenhour, Cadden and Schaffer [37] (1942).

III. Toxic Nephrosis

(*a*) *Vitamin D Intoxication.* In a previous report (Corcoran, Taylor and Page, 1943 [27]) we have discussed the course and probable interpretation of the renal functional changes occurring during toxic nephrosis due to inhalation of carbon tetrachloride. In this report we noted the similar patterns of injury in toxic nephrosis due to mercuric chloride and to oil of tansy. We therefore omit consideration of these conditions and shall only describe in this report the patterns found in renal injury due to vitamin D intoxication.

Observations were made in two patients during the course of an illness characterized by malaise, nausea and vomiting, evidences of renal impairment, metastatic vascular calcification and hypercalcemia which appeared during treatment with a product of the irradiation of ergosterol (Ertron). Clinical details of those and other similar cases form the substance of another report. The renal functional patterns in these two patients are shown in table 6b.

The pattern resembles that of other toxic nephroses. The predominance of tubular injury is indicated by the high ratios GFR/Tm_D, which is the reverse of the change frequently found in acute and sub-terminal chronic glomerulonephritis. Withdrawal of the medication and symptomatic treatment has resulted in the recovery of these patients. The pattern during healing is shown for patient No. 41 seven months after the first observation. Evidence of healing in patient No. 40 consists in a urea clearance of 65 per cent of normal and a maximum urinary specific gravity of 1.024 eight months after the first observation.

(*b*) *Hemoglobinuric Nephrosis.* Experimental observations on the nature of the renal functional injury caused by administration of myoglobin and hemoglobin to dogs has been reported previously (Corcoran and Page,[39] 1945). These observations indicate that the renal lesion, which is not commonly severe, is partially due to obstruction of tubules by pigment deposits and partly to cytotoxic tubular changes. The latter are attributed to ingestion of the heme-pigments by the cells of the proximal tubules. The renal function most affected is Tm_D.

Summary

The renal functional pattern of toxic nephrosis is one of depression of all functions, principally of Tm_D. Their nature demands great caution in interpretations of clearances determined in these states. Indeed, it has been shown that the interpretation usually attributed to plasma clearances of inulin

or diodrast are vitiated in such an experimental toxic nephrosis as that due to uranium nitrate (Bobey, Longley, Dicker, Price and Hayman,[40] 1943). The fallacy depends on loss of the selective permeability of renal tubules.

IV. Functional Disorders

The patterns of discrete renal functions are especially useful in characterizing renal disorders which are functional.

Thus, observations made during water deprivation, with consequent oliguria in young men (McCance, Young and Black,[41] 1944) have shown that renal blood flow and glomerular filtration are normal. The only change is increased reabsorption of water. In clinical "dehydration" with loss of interstitial fluid and plasma volume, both renal blood flow and glomerular filtration are reversibly depressed.

Shock. The same changes occur in both experimental (Corcoran and Page,[42] 1943a; Corcoran, Taylor, and Page,[43] 1943b; Phillips, Dole, Hamilton, Emerson, Archibald and Van Slyke,[44] 1945) and clinical (Lauson, Bradley and Cournand,[53] 1944) shock. The renal change which presages the onset of shock is a decrease of renal blood flow due to increased vascular resistance. A similar pattern is observed after severe gastrointestinal hemorrhage (Black, Powell and Smith,[46] 1941). The renal vasoconstriction is attributed by us largely to the action of a humoral vasoconstrictor entering the blood stream from injured tissues, other than liver or kidney. In sèvere shock the interpretation of the pattern is obscured, partly because of a redistribution of renal blood flow. This change may depend on shunting of blood from renal cortex to medulla, ascribed (Trueta, Barclay, Daniel, Franklin, and Pritchard,[51] 1947) to vasomotor stimulation. But part of the abnormality of the pattern is probably dependent on altered permeability of tubules due to prolonged renal ischemia (Selkurt,[45] 1945).

These renal changes in shock are the basis of the severe renal failure of crush syndrome and related states, i.e., of the lower nephron nephrosis of Lucké [47] (1946). In most of these conditions renal failure is dependent on the superimposition of pigmentary precipitation on renal vasoconstrictive ischemia (Corcoran and Page,[48] 1947).

Arterial Hypotension. Because they illustrate the application of these procedures to functional disorders, we recapitulate observations made during hypotension due to ingestion of arsenic trioxide (Page, Taylor and Kohlstaedt) and idiopathic orthostatic hypotension (Corcoran, Browning and Page,[49] 1942).

The observations are summarized in table 6c. Minimal renal blood flow was maintained at a level of about two-thirds normal during severe hypotension due to arsenic. This rate of perfusion is sufficient to sustain normal tubular secretory activity, as is indicated by the level of Tm_D. While the level of arterial pressure (48 mm. Hg) found during the clearance test is usually insufficient to maintain glomerular filtration, the rate of filtration was measured at about one-third normal. The derived functions FF and GFR/

Tm_D are also one-third normal. Calculation of resistances by the method of Lamport is impossible in this case, presumably because the greatly altered conditions changed the values allowed for yield pressure and tissue pressure in the equations. However, the maintenance of blood flow and filtration in the face of severe arterial hypotension testify to an extensive renal vasodilation. That peripheral vasodilation was present in a large vascular bed was confirmed by clinical examination and by the ballistocardiographic demonstration of a great increase in cardiac output.

These changes contrast with those found during orthostatic hypotension. In the patient under observation, this state appeared after an exhausting illness. The control levels of the renal functions were uniformly depressed. Tilting to 60° resulted in arterial hypotension. This was associated with decreases in RBF and GFR (Tm_D was not measured but is assumed to be unchanged). FF was unchanged. Calculation of resistance indicates that the maintenance of FF is due to intraglomerular pressure having been sustained by efferent arteriolar constriction. Thus, the renal hemodynamic pattern in this hypotensive state contrasts markedly with the toxic vasodilation present in arsenic poisoning.

General Summary

From observations in a wide variety of disorders which affect renal function, we summarize determinations of renal blood flow, glomerular filtration rate and tubular secretory capacity. The summaries consist in patterns of altered function which are shown to correspond with clinical, physiological and pathological estimates of the underlying renal changes, functional and structural.

The largest series of observations was made in patients suffering from hypertensive vascular diseases. The conclusions drawn are (*a*) that early essential hypertension is a functional disorder in which the only measurable renal abnormality is an increase of afferent resistance, presumably due to afferent arteriolar constriction, but that (*b*) as the process advances and evidences of extra-renal vascular damage appear, renal vasoconstriction becomes more intense, extends to both afferent and efferent arterioles, often results in renal ischemia and is associated with renal arteriolar sclerosis and resultant loss of secretory tissue. (*c*) In essence, the pattern in malignant hypertension is an exaggeration of these changes, characterized by rapid advance, but not, at its outset, associated with or caused by excretory insufficiency. By way of corollaries, we note that essential hypertension cannot be regarded as due to renal ischemia nor as a compensation for increased renal resistance due to vascular sclerosis and obliteration. (*d*) Arteriosclerotic hypertension is found to be associated with renal changes consistent with focal obliteration of afferent arterial channels.

In considering other diseases associated with arterial hypertension, attention is directed to the pattern in Cushing's syndrome, which is similar to

that of essential hypertension, but, in this small group, comparatively severe.

We note the diverse patterns in chronic pyelonephritis. When this condition is associated with arterial hypertension, the pattern is that of essential hypertension. Normotensive patients suffering from chronic pyelonephritis show a simple loss of function. Patients in whom the disease is active show patterns indicative of increased renal interstitial pressure, together with a severe loss of tubular function.

In diffuse glomerulonephritis, the renal pattern in the acute stage is shown to be one essentially of interference with glomerular filtration but with widely varying levels of blood flow and other functions which return towards normal during healing. The pattern in chronic glomerulonephritis is similar until the end stage when there is a very severe loss of tubular secretory tissue. The renal pattern in intercapillary glomerulosclerosis is shown to resemble that of chronic glomerulonephritis. That of specific toxemia of pregnancy is similar to that of acute glomerulonephritis.

In the toxic nephroses, the predominance of tubular injury is demonstrated in cases of vitamin D intoxication, and reference is made to findings in experimental hemoglobinuric nephrosis.

Finally, we contrast observations in orthostatic hypotension, in which there is little renal vasodilation, with those of hypotension due to arsenical intoxication, in which there is a severe renal vasodilation.

Thus, in a number of clinical disorders affecting renal function, the information yielded by the new tests of renal function is shown to indicate the nature of the changes occurring in the kidney. The estimates obtained from such studies are more precise, as regards circulatory and excretory aspects of renal function, than any which can be derived in the functional assay of other organs by present methods.

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CLINICAL APPRAISAL OF BENADRYL, PYRIBENZAMINE, AND ANTHALLAN IN THE TREATMENT OF ALLERGIC DISORDERS *

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DURING the past year there have been numerous reports of remarkable advances in the treatment of various types of allergic reactions through the use of three drugs in particular which appear to have the action of neutralizing the effects of histamine. I refer to the new "antihistamine" preparations that have become available: Benadryl, Pyribenzamine, and Anthallan. The therapeutic usefulness of these pharmaceuticals has led to widespread acclaim by the laity, to hundreds of back orders in drug stores, and to exaggerated propaganda by the press and radio. This was particularly true during the dreaded hay-fever season when untold numbers of sufferers were told of the new "allergic panacea" of medical science. Internists in particular feared that indiscriminate use of the drugs might outweigh whatever beneficial effects they might possess.

For the most part, it is assumed that the liberation of histamine in sufficient concentration accounts for the signs and symptoms of anaphylaxis and allergic reactions.[1] Histamine is known to produce contraction of smooth muscle, especially in the bronchioles, blood vessels, intestines, and uterus; to cause dilatation and increased permeability of the capillaries of the skin and mucous membranes; to act as a secretogogue in the glands of exocrine secretion such as the salivary, gastric, intestinal, pancreatic, and the respiratory tract glands; and lastly to induce pain at the site of injection in the skin.[2] It is reported that histamine appears in the blood immediately after the administration of an antigen, and that in the guinea pig the phenomena of anaphylaxis and those following the administration of histamine are identical.[3]

The production of an allergic state results from the linkage of certain fixed cells or antibodies with a specific antigen, from which union there results a liberation of histamine. It has been stressed in the past that allergy is not a single or uniform biologic phenomenon. There are different varieties of anaphylaxes varying from an induced physiological allergy, such as serum sickness or bacterial sensitivity, to a spontaneous, pathologic or hereditary allergy exemplified by hay-fever or angioneurotic edema.[4] The etiologic agents concerned in allergic reactions are well known.

Although it has generally been considered that a trial with an antihistamine substance would lead to interesting results in the treatment of allergic manifestations, it was not until recently that Loew, Kaiser, and

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Moore [5, 6] discovered that, of all the synthetic benzhydryl alkamine ethers used in alleviating anaphylaxis and histamine shock in experimental animals, betadimethylaminoethyl benzhydryl ether hydrochloride (Benadryl) was the most effective studied. It appeared to be more effective than theophylline-ethylene diamine (Aminophylline) in relieving bronchial constriction and diminishing the depressor effects of histamine and acetylcholine while alleviating the vasopressor effects of histamine and smooth muscle spasm. McElin and Horton [7] of the Mayo Clinic report convincing experimental evidence demonstrating the ability of Benadryl to combat certain actions of histamine such as vasodilatation, histamine-induced nasal congestion, and rise in gastric acidity. They review a small series of allergic cases, in which both oral and parenteral Benadryl were administered. The latter technic was used in experimental cases, and excellent results were obtained in a large majority of instances. They discovered that sleepiness, dizziness, dry mouth, nervousness, and urinary frequency were the predominant side effects of the drug.

O'Leary and Farber [8] found that Benadryl was extremely effective in the treatment of urticaria and angioneurotic edema. They found the drug only palliative in effect, though it produced complete relief in 34 of a series of 50 patients and definite improvement in 12. The use of Benadryl in hay-fever and bronchial asthma has been thoroughly studied. One group found it benefited 75 per cent of hay-fever patients, 74 per cent of patients having concomitant hay-fever and asthma, and 33 per cent of cases of bronchial asthma.[9] Williams found Benadryl to be effective in treating physical allergy of the head, especially vasomotor rhinitis.[10] Logan has employed Benadryl successfully in the treatment of allergic conditions of childhood.[11] In a very early report on the use of this drug Curtis and Owens [12] administered Benadryl to 18 patients who had acute and chronic urticaria and noted immediate relief of signs and symptoms in 11, definite improvement in three, and no benefit whatsoever in four. In an excellent article Code [1] reviews the pharmacology of Benadryl and its action as an antihistamine substance. He implies that there is still much to be understood in histamine metabolism and in the interpretation of the action of Benadryl before one comes to definite conclusions regarding its properties. Friedlander and Feinberg [13] have stated that Benadryl given orally causes slight inhibition of histamine wheal, whereas a marked reduction follows its local application. It is interesting to note that these investigators actually found Benadryl, in a single oral dose of 100 mg., to cause a slight reduction in both systolic and diastolic blood pressures for several hours. They remark that this phenomenon was central in origin as is the side effect of drowsiness. Thacker,[14] in a very well organized survey, found Benadryl to offer 30 per cent complete relief, 20 per cent definite improvement, and 50 per cent slight or no benefit in the treatment of vasomotor rhinitis; and 28.5 per cent complete relief, 14.3 per cent definite improvement, and 57.1 per cent slight or no benefit in the treatment of perennial allergic rhinitis. Only half of his patients with allergic rhinitis

and bronchial asthma manifested definite improvement. This series, however, was unfortunately small in number.

Waldbott,[15] in treating 165 cases of urticaria with Benadryl, found complete relief in 80 per cent of cases treated. In this series relief was afforded within four hours after oral administration of one capsule. He found Benadryl to effect complete relief in 32 per cent and partial relief in 18 per cent of cases with perennial bronchial asthma; 30 per cent and 16 per cent in seasonal bronchial asthma; 51 per cent and 23 per cent in hay-fever; and 43 per cent and 31 per cent in vasomotor rhinitis. On the bases of this experience he considered the effect of the drug to be more pronounced on the allergic wheal than on bronchospasm. Eyermann [16] gave Benadryl to a series of 52 patients with vasomotor rhinitis and found that 67 per cent experienced complete relief, and that sneezing was abated in the remaining 23 per cent. One report deals with the successful treatment of an insulin allergy with Benadryl.[17] O'Leary and Farber [18] have successfully treated urticaria, scleroderma, and allied dermatoses with large doses of oral Benadryl but caution against the indiscriminate use of the drug because of the severe side reactions. Feinberg [19] insinuates that Benadryl gives no lasting benefit but only palliative effect; he likewise stresses limitations of the drug because of the undesirable side reactions. Sixty per cent of Levin's series manifested the side effect of drowsiness, and the withdrawal of the drug led to symptomatic relapse.[20] Schwartz and Levin [21] have used Benadryl with reasonable success in a small series of allergic disorders. Numerous other reports concerning the therapeutic value of Benadryl are available, though the efficacy of this drug in the treatment of dysmenorrhea, migraine, and various cutaneous disorders is questionable.

Mayer [22] lists two main groups of substances exhibiting antihistamine properties: (1) amino acids such as arginine, histidine, and cysteine, and (2) certain aromatic derivatives of amino-ethanol and ethylene-diamine. He advances a hypothesis that these antihistamine substances compete with histamine to displace it from the site of action, similarly to the action of para-amino-benzoic acid in the displacement of the sulfonamide drugs. He believes that the action of the anti-histamine substances is upon what, according to the theory of histamine effect, is the last phase of the allergic or anaphylactic reaction. Feinberg,[23] in a recent report concerning the experimental and therapeutic status of histamine and antihistamine drugs, mentions the relative merits of the recent French antihistamine agents, namely the Fourneau and Mosnier compounds, and concludes that their toxicity is too great to warrant their therapeutic use. His article is a brilliant, comprehensive review of the recent pharmacological aspects of allergy control.

Ciba Pharmaceutical Products, Inc., have introduced Pyribenzamine Hydrochloride, chemically N′-pyridyl-N′-benzyl-N-dimethyl ethylene diamine hydrochloride. This product, like Benadryl, is a white crystalline substance, is stable, and is readily soluble in water; it has been shown to counteract histamine intestinal spasm, histamine asthma, histamine shock, anaphylactic

shock, and to abolish histamine skin wheals in experimental animals. Whereas Benadryl is supplied in both 25 mg. and 50 mg. capsules and in an elixir vehicle by the Parke, Davis & Company, Pyribenzamine at present is dispensed in 50 mg. tablet form.[24] Arbesman, Koepf, and Miller [25] found Pyribenzamine to have variable antianaphylactic activity, though exhibiting no demonstrable effect on the precipitin or complement titer in guinea pigs. When this drug was administered orally 18 out of 28 subjects presented decreased histamine wheals. These investigators disclosed diminished skin reactivity in 14 out of 24 allergic patients, and also a reduced reactivity of the skin sites which were passively sensitized with serum containing cottonseed reagins. They found improvement with Pyribenzamine in 95 per cent of cases of acute urticaria, 70 per cent of cases of chronic urticaria, 85 per cent of cases of seasonal hay-fever, 73 per cent of cases of extrinsic rhinitis, 50 per cent of cases of intrinsic rhinitis, 50 per cent of cases of seasonal bronchial asthma, 49 per cent of cases of extrinsic non-seasonal bronchial asthma, and 25 per cent of cases of intrinsic non-seasonal bronchial asthma. Epstein [26] found Pyribenzamine to afford excellent relief in the treatment of acute and chronic urticaria and atopic dermatitis. Osborne, Jordan, and Rausch [27] list Pyribenzamine as a successful agent in the treatment of certain allergic disorders including chronic atopic dermatitis, physical allergy, and dermatitis herpetiformis. The predominant side effects reported were of less severity than those observed with the use of Benadryl. Minor side reactions have been reported in 30 per cent of cases, the most frequent of which were drowsiness, nausea, headache, dizziness, dryness of the mouth, nervousness, and abdominal discomfort, in the order given. The recommended dosage has been the same as Benadryl, 50 mg., but because of individual variation as little as 50 mg. and as high as 600 mg. have been used.[24] For most patients 50 mg. twice to four times daily after meals usually suffices.

The third product just recently made available to the medical profession for the treatment of allergic rhinitis and allergic skin manifestations is Anthallan, a synthetic organic substance with chemical formula of 3′-di(n-butyl)amino-methyl-4,5,6-trihydroxy-benzo-(1,2,-c)furan-1′(3′)-one, $C_{17}H_{23}O_5H$; it is a lactone of beta-gallic acid-ethanol-alpha-di(n-butyl)amine. The mild antihistamine action of Anthallan is based on the fact that it antagonizes lethal doses of histamine in guinea pigs, causes abolition or suppression of histamine-induced spasms in guinea pig uterus or intestine, diminishes the vasopressor action of histamine, manifests rebound blood pressure rise after primary histamine lowering of blood pressure, and suppresses anaphylactic shock in sensitized guinea pigs. This drug is relatively non-toxic, and no intolerance to it has been observed in experimental animals.[28] Ghiselin [29] has reported a series of 48 seasonal and non-seasonal allergic rhinitis cases in which Anthallan was administered. In an elaborate method of grading the degree of improvement registered by each patient, this report discloses that benefit from Anthallan was found in 90 per cent of patients studied, the improvement varying between 25 and 100 per cent objectively and sub-

jectively. The controlling factor in this experiment has been questioned, and the newly coined term, "hyperesthetic rhinitis," has met with some disapproval.[30] Results in the Ghiselin trials were obtained over a period of seven to 35 days in patients selected on the basis of certain diagnostic criteria. Frequently the degree of improvement could be noticed within the first week. No significant variation in laboratory findings was observed, and the only side reactions noticed were one case of diarrhea and one of acute dermatitis. Schwartzschild [31] used Anthallan to treat 35 cases of neurodermatitis disseminata, 41 cases of urticaria, and eight cases of papular urticaria, all of which were resistant to or unimproved by other types of therapy. In this significant series benefit was found in 80 per cent of cases, the improvement varying between 50 to 100 per cent by scale. One case developed an attack of diarrhea which subsided upon discontinuation of Anthallan. A complete and persistent subsidence of infantile eczema in twins after three weeks of treatment employing Anthallan is reported.[28] Ereaux and Craig [32] have used Anthallan successfully in treating infantile eczema and atopic dermatitis. Particularly large doses were used in this series of cases.

Anthallan is supplied in individual capsules containing 85 mg. of the drug, the recommended oral dosage being two capsules after each meal. A three weeks' course of therapy is suggested, and in a surprising number of cases, particularly infantile eczema and atopic dermatitis, permanent cure results. Though this drug possesses mild antihistamine properties, its mode of action still remains obscure. Many unsuccessful courses of treatment have been the result of inadequate dosage, and initial large doses of Anthallan are advised until a smaller maintenance dose can be managed after several weeks. It is important that all infectious cases be eliminated before Anthallan is administered so as to assure consistent results. The research division of the Medico Chemical Corporation of America, manufacturers of Anthallan, has reported several cures of allergic skin disorders within recent months.[28]

Clinical Studies

The purpose of these studies was to test the efficacy of Benadryl, Pyribenzamine, and Anthallan in the treatment of various common allergic disorders. The author feels that the current widespread indiscriminate use of these products without proper attention to a thorough allergic examination constitutes a definite danger. The work here reported was carried out at the Umatilla Ordnance Depot, Ordnance, Oregon, where the author was Post Surgeon at an active station hospital. Here the situation was particularly favorable for observing cases of hay-fever, asthma, and various perennial allergic manifestations, as the depot is located on a large plateau of sand and desert weeds, and, because of the continuous activity of the wind, pollens, dust, and animal emanations are widely disseminated throughout the countryside. All allergic cases were studied completely. The following routine examinations were carried out in order effectively to standardize the series:

physical examination, routine laboratory studies, nasal smears including determination of eosinophilia, sinus and chest roentgenograms when indicated, cutaneous skin tests for specific allergens in many cases, and a complete otorhinolaryngological examination. For the most part the patients had never been desensitized and were not taking concomitant therapy at the time of the experiment except vasoconstrictor nose-drops or patented ephedrine-phenobarbital tablets in a few cases. An extensive history was taken in an attempt to discover seasonal variation, familio-hereditary traits, and the type and onset of discomfort. The patients were either military personnel, laborers at the depot, or civilians living in the area. Excellent coöperation by all patients was obtained throughout the trial test, and none had the opportunity of altering his environment. Every patient had the procedure completely explained to him and was instructed to eliminate any extraneous factors, such as noxious fumes, irritating gases, paints, etc., that would interfere with the end results of the experiment. Often throughout the course placebos were administered in a manner which effectively concealed their identity. For example, when drowsiness became an outstanding side reaction, 60 mg. of phenobarbital was given orally and the consequences noted. As the terminology "vasomotor rhinitis" is often misinterpreted, the following diagnostic criteria (Thacker [33]) were used: (1) intermittent nasal congestion, alternating or bilateral, for one year or more; (2) normal appearance of the mucosa of the turbinates, which, if slightly hyperemic, demonstrated little or no excess nasal secretion; (3) enlarged turbinates which shrank well with vasoconstrictor medicaments; (4) negative history for allergy, negative nasal smears for eosinophiles, and cutaneous tests which revealed no sensitivity.[14] In addition to the above criteria, cases were selected for study that were relatively free of emotional disturbance or nervous tension which might interfere with their existing disorder. For each drug the minimal length of the test period was 21 days, the average time being 30 days. Using the aforementioned criteria 170 cases were selected from available clinical material, eight of which were subsequently used for control purposes. In many cases, after results were assured with a particular drug, a short period of time would be allowed to elapse before trial of another drug. In a small series of cases successive trials of the three drugs were successfully accomplished. Patients were interviewed and examined twice a week to determine the degree of palliation afforded by the drug and the occurrence of side effects.

The clinical results in 106 cases of allergic disorders treated with oral Benadryl are tabulated in table 1. By comparing the figures, it may be stated that there is evidence that Benadryl alleviates the histamine wheal more effectively than it abolishes bronchospasm. Benadryl produced effective palliation in seasonal allergic rhinitis (grasses-ragweed), angioneurotic edema of the skin, and acute urticaria, but was less beneficial in perennial allergic rhinitis, vasomotor rhinitis, and seasonal allergic rhinitis with bronchial asthma. It was least effective in seasonal bronchial asthma. Although sufficient relief was afforded patients with atopic dermatitis, the

small number of cases studied introduces a wide margin of error. Although the average dosage of Benadryl used was 100 mg. daily, it was found necessary to raise the dosage to 150 mg. in cases of seasonal allergic rhinitis with bronchial asthma, vasomotor rhinitis, and angioneurotic edema. Urticaria and angioneurotic edema disappeared completely within four to six hours, whereas 48 to 72 hours were required for the cutaneous remission of atopic dermatitis. Continuous therapy was necessary to avoid relapses in the latter condition. Seasonal bronchial asthma necessitated the administration of an average of 50 mg. four times a day, and patients were often compelled to increase this amount to 300 mg. daily. It is interesting to note that in 8 per cent of the cases complete failures occurred in treating seasonal bronchial asthma with Benadryl, whereas no failures were encountered in treating the other allergic disorders. Most patients found that taking 50 to 100

TABLE I

Clinical Results with Benadryl

Predominant Allergic Manifestations	No. of Cases	Aver. Yrs. Symptom	Aver. Daily Dosage	Aver. Yrs. Age	Degree Relief Afforded			
					Great	Mod.	Slight	None
1. Seasonal Allergic Rhinitis (Grasses-Ragweed)	39	11	100 mg.	34	31 (80%)	6 (15%)	2 (5%)	0
2. Vasomotor Rhinitis	10	14	150 mg.	27	6 (60%)	3 (30%)	1 (10%)	0
3. Perennial Allergic Rhinitis (Extrinsic-Intrinsic)	21	10	100 mg.	28	15 (71%)	4 (19%)	3 (10%)	0
4. Seasonal Allergic Rhinitis with Bronchial Asthma	22	12	150 mg.	32	14 (64%)	6 (27%)	2 (9%)	0
5. Seasonal Bronchial Asthma	12	12	200 mg.	26	6 (50%)	3 (25%)	2 (17%)	1 (8%)
6. Angioneurotic Edema (Skin)	4	3	150 mg.	24	4 (100%)	0	0	0
7. Acute Urticaria	6	5	100 mg.	27	5 (83%)	1 (17%)	0	0
8. Atopic Dermatitis	2	4	100 mg.	34	1 (50%)	1 (50%)	0	0

mg. of Benadryl prior to sleep aided remarkably in combating nocturnal asthma. For the most part patients expressed the opinion that palliation of symptoms occurred generally within one hour after ingestion of the drug, the effects lasting three to four hours. It was found that Benadryl could prevent asthmatic attacks, but the oral route was ineffective in aborting a sudden attack. As this series deals only with Benadryl, mention will be made in later pages concerning the wisdom of concomitant therapy. Although not the immediate subject of this study it is worthwhile to note that Benadryl in average doses was found effective in treating drug idiosyncrasies such as barbiturate or iodide cutaneous reactions, serum sickness and urticaria from tetanus antitoxin, acute urticaria and bullous dermatitis from penicillin sensitization, and food allergy. Moderate to slight relief was afforded patients with allergic bronchitis, severe intrinsic bronchial asthma, migraine, and Ménière's disease.

One hundred and 11 cases of allergic disorders were treated with Pyribenzamine, and here again it was noticed that the histamine wheal was more effectively abolished than bronchospasm. Thus, in hay-fever, perennial allergic rhinitis, acute urticaria, and atopic dermatitis, outstanding palliative results were obtained, but seasonal allergic rhinitis in combination with bronchial asthma and uncomplicated bronchial asthma were afforded less relief. It is interesting to note that 7 per cent of the failures were found in seasonal allergic rhinitis (grasses-ragweed). Fifty per cent of cases of vasomotor rhinitis experienced complete relief, and another 25 per cent experienced moderate to slight relief from Pyribenzamine therapy. Whereas a greater number of complete failures were observed with Pyribenzamine than with Benadryl in alleviating the distressing symptoms of seasonal bronchial asthma, there was a greater incidence of moderate and slight relief noted. The average dosage of Pyribenzamine was 200 mg. daily divided into four equal doses. The alleviation of rhinorrhea and conjunctival irritation in seasonal allergic rhinitis could be accomplished with 150 mg. of Pyribenzamine. There was little variation in the degree of relief afforded patients suffering from seasonal allergic rhinitis with bronchial asthma by administering 300 mg. instead of the recommended 200 mg. It was necessary for the most part to treat bronchial asthmatics with 300 mg. of Pyribenzamine daily, and often another 50 to 100 mg. was used prior to bedtime to abate any nocturnal asthma. Although 100 per cent of cases of atopic dermatitis experienced great relief with Pyribenzamine within several days, obviously the number of cases is too small to make any generalization. Continuous therapy was necessary to avoid relapses. Patients noted palliation of symptoms from Pyribenzamine within 45 minutes to an hour following administration, and the length of relief was usually three to four hours. Similarly,

TABLE II

Clinical Results with Pyribenzamine *

Predominant Allergic Manifestations	No. of Cases	Aver. Yrs. Symptoms	Aver. Daily Dosage	Aver. Yrs. Age	Degree Relief Afforded			
					Great	Mod.	Slight	None
1. Seasonal Allergic Rhinitis (Grasses-Ragweed)	42	12	150 mg.	32	30 (72%)	6 (14%)	3 (7%)	3 (7%)
2. Vasomotor Rhinitis	8	13	200 mg.	36	4 (50%)	2 (25%)	2 (25%)	0
3. Perennial Allergic Rhinitis (Extrinsic-Intrinsic)	20	11	200 mg.	28	16 (80%)	3 (15%)	1 (5%)	0
4. Seasonal Allergic Rhinitis with Bronchial Asthma	22	10	200 mg.	30	8 (36%)	10 (46%)	4 (18%)	0
5. Seasonal Bronchial Asthma	21	14	300 mg.	38	1 (8%)	3 (25%)	6 (50%)	2 (17%)
6. Acute Urticaria	5	5	200 mg.	27	4 (80%)	1 (20%)	0	0
7. Atopic Dermatitis	2	4	200 mg.	34	2 (100%)	0	0	0

* Pyribenzamine Hydrochloride was generously supplied by the Ciba Pharmaceutical Products Inc., Summit, N. J.

Pyribenzamine was noted to act better as a prophylactic agent against bronchial asthma than in treatment of an asthmatic attack.

The third drug that was clinically tested on allergic disorders was Anthallan, but because of the limited amount available at the time of the experiment a considerably smaller number of cases was studied. In comparison with the other antihistamine drugs, this substance is, on the whole, untested in clinical cases; therefore, every attempt was made to keep the experiment rigidly controlled, and meticulous care was exercised to eliminate any extraneous factors that would alter the results in this small series of cases. Anthallan was found to exhibit very weak antihistamine properties, having practically no antibronchospastic qualities. This is in agreement with the findings of other investigators.[28] The dosage used was two 85 mg. capsules three times a day. This was the minimum dose, and most often it was raised whenever inadequate results were secured. For the first two to three weeks this routine was maintained, and, in most subjects with the exception of bronchial asthmatics, it was soon found that a maintenance dose of one capsule three times daily could eventually be employed. Cases of seasonal allergic rhinitis, perennial allergic rhinitis, acute urticaria, and atopic dermatitis responded quite effectively to Anthallan. I feel that any failures occurring with this drug, excluding bronchial asthma cases, could probably be minimized if larger doses over a longer period of time were used. The failure in 17 per cent of vasomotor rhinitis cases is significant, and the complete failure of Anthallan to prevent asthmatic attacks again indicates its apparent weak antihistamine character. Half of the patients treated with Anthallan had previously been tried with Benadryl or Pyribenzamine for a period of not over three weeks during the height of the seasonal pollination, a rest period from three to five days being permitted before clinical comparison with Anthallan. This procedure was followed to minimize the clinical error. Although satisfactory results were obtained in relieving cases of urticaria and atopic dermatitis, the number of cases again is too small for any general conclusions to be drawn. However, my experience with Anthallan, since the time of the study, in regard to acute and chronic urticaria, angioneurotic edema, atopic dermatitis, and two cases of drug idiosyncrasy leads me to believe that Anthallan is invaluable in the treatment of these disorders, particularly since no toxic reactions from the drug have been personally witnessed.

It was noted that the major disadvantage with both Benadryl and Pyribenzamine is the large number of undesirable and uncomfortable side reactions that were prevalent. In this investigation Benadryl was found to give almost twice the number of side reactions as Pyribenzamine. In the former series, 72 per cent of the cases exhibited them as against 43 per cent for the Pyribenzamine series. In agreement with other investigators, it was discovered that somnolence, fatigability, dry mouth, dizziness, urinary frequency, feeling of nervousness, and epigastric distress were the predominant side effects for both drugs with the possible exception of dizziness which was

found in only 2 per cent of the Pyribenzamine series. Other less common side reactions are listed in table 4, and it is noted that tinnitus, shortness of breath, pallor, blurred vision, and palpitation were encountered only with Benadryl. Two cases treated with Benadryl and one case with Pyribenzamine were forced to discontinue treatment because of exhaustion; in addition one case of narcolepsy was observed with Benadryl. Peculiarly enough it was found that children were more immune to side reactions from both Benadryl and Pyribenzamine than adults, the dosage having no bearing on the case. In a great many cases tolerance to side reactions would develop after several days of therapy. Often the administration of caffeine tablets, a cup of strong tea or coffee, or 10 mg. of amphetamine sulfate (Benzedrine) was used to combat drowsiness, and in particular fatigue. Though the ana-

TABLE III

Clinical Results with Anthallan *

Predominant Allergic Manifestations	No. of Cases	Aver. Yrs. Symptoms	Aver. Daily Dosage	Aver. Yrs. Age	Degree Relief Afforded			
					Great	Mod.	Slight	None
1. Seasonal Allergic Rhinitis (Grasses-Ragweed)	22	11	.51 gm.	34	14 (64%)	4 (18%)	2 (9%)	2 (9%)
2. Vasomotor Rhinitis	6	14	.51 gm.	26	1 (17%)	1 (17%)	3 (50%)	1 (17%)
3. Seasonal Allergic Rhinitis with Bronchial Asthma	18	10	.51 gm.	32	4 (22%)	5 (28%)	4 (22%)	5 (28%)
4. Perennial Allergic Rhinitis (Extrinsic-Intrinsic)	12	8	.51 gm.	22	9 (75%)	2 (17%)	1 (8%)	0
5. Seasonal Bronchial Asthma	10	12	.51 gm.	38	0	1 (10%)	5 (50%)	4 (40%)
6. Acute Urticaria	2	2	.51 gm.	34	2 (100%)	0	0	0
7. Atopic Dermatitis	3	4	.51 gm.	27	2 (67%)	1 (33%)	0	0

* Anthallan was generously supplied by the Medico Chemical Corporation of America, New York, N. Y.

leptic and sympathomimetic properties of the latter drug were realized, in no case was there noted any exacerbation of the underlying allergic disorder. Particularly in employing Benadryl, it was noted in some cases that side reactions were definitely the result of overdosage, and proper adjustment was effectively made. Somnolence, fatigability, dizziness, and nervousness in particular can endanger the patient's welfare during the course of his daily routine. Benadryl was found to be the contributing cause to an industrial accident.[34] Shocklike reaction,[35] epileptiform seizure,[36] prolonged reaction,[37] and the danger of self medication and large dosage [38] are but a few recently reported severe dangers from Benadryl therapy. For this reason the administration of Benadryl should always be under a physician's guidance.

In the series treated with Anthallan there was no evidence of side reactions. This made utilization of the drug exceedingly advantageous. Perhaps this is explained by the low antihistamine property of the drug. One

case of nausea from Anthallan was cured when the capsules were administered following meals according to the general directions for use of the drug.

The use of Benadryl, Pyribenzamine, and Anthallan is a valuable contribution in symptomatic control over several allergic disorders, but these drugs are not a substitute for a complete history and physical examination, adequate laboratory procedures, allergic skin tests, and roentgenograms of the sinuses and chest or anything conducive to a complete allergic study of the patient. The neglect of such basic procedures is apt to become the most serious disadvantage resulting from the introduction of the antihistamine drugs. These drugs are no substitute for desensitization to an offending allergen or a change from a particularly unfavorable environment. They may be considered as only a valuable adjunct to any allergic régime. Often concomitant therapy should be considered. The use of vasoconstrictor nose drops as a temporary relief from nasal congestion may be considered, but the patient must be warned that overuse of these is a dangerous procedure. Rhinitis medicamentosa is a severe consequence that is commonly encountered in the treatment of chronic nasal obstruction.[39] The use of expectorants particularly in allergic bronchitis and bronchial asthma as concurrent therapy with the antihistamine drugs was found very effective. In this respect

TABLE IV

Comparative Incidence of Side Reactions

Side Reactions	Benadryl (Average Dosage 100 mg. daily; 96 cases)	Pyribenzamine (Average Dosage 200 mg. daily; 91 cases)
1. Somnolence	62 cases (65%)	24 cases (26%)
2. Fatigability	54 cases (56%)	12 cases (13%)
3. Dry Mouth	52 cases (54%)	22 cases (13%)
4. Dizziness	29 cases (30%)	2 cases (2%)
5. Urinary Frequency	14 cases (15%)	13 cases (14%)
6. Nervousness	12 cases (13%)	12 cases (13%)
7. Epigastric Discomfort	6 cases (6%)	4 cases (4%)
8. Headache	3 cases (3%)	4 cases (4%)
9. Bad Taste	3 cases (3%)	4 cases (4%)
10. Nausea	3 cases (3%)	1 case (1%)
11. Tinnitus	2 cases (2%)	0
12. Discontinuation of Drug	3 cases (3%)	1 case (1%)
13. Shortness of Breath	1 case (1%)	0
14. Pallor	1 case (1%)	0
15. Exhaustion	1 case (1%)	1 case (1%)
16. Blurred Vision	1 case (1%)	0
17. Palpitation	1 case (1%)	0
18. Hot Flashes	1 case (1%)	1 case (1%)
19. Coldness of Extremities	1 case (1%)	1 case (1%)
20. Confusion	1 case (1%)	0
21. No Side Reactions	27 cases (28%)	52 cases (57%)

potassium iodide, ammonium chloride, or elixir of terpin hydrate were utilized. Aminophylline in doses of 0.2 gm. orally may act synergistically in relieving bronchospasm; nadin may be employed with reasonable success. The use of hapamine with the antihistamine drugs is as yet untried. Nonspecific desensitization with histamine diphosphate has been disappointing in treating allergic disorders, although it has cured migraine and histamine cephalalgia successfully. It has been my experience that a low sodium, high

potassium régime produces minimal effect, if any at all, in relieving allergic trouble. Thacker,[33] in a complete survey of chronic nasal obstruction, has recommended highly the injection of the turbinates with sclerosing solutions, if less radical measures fail to afford proper relief. The indiscriminate use of vasoconstrictor-sulfonamide, tyrothricin, or penicillin nose drops should be avoided because of the possible development of bacterial fastness. Investigation of the functional or psychiatric factor in allergic diseases is of paramount importance, and control of this can be considered as valuable as relief of organic distress. Lastly, a proper, well-balanced diet, adequate rest, and good hygiene is most desirable. These are some of the palliative measures that may be effectively used in conjunction with the new antihistamine drugs.

The advent of Benadryl, Pyribenzamine, and Anthallan is a major step in conquering the distressing symptoms of hay-fever and other allergic reactions. They are by no means a panacea and offer only palliative effects, but they are the first antihistamine drugs that have met with reasonable success in treating a wide variety of allergic disorders. The accompanying tables demonstrate their comparative effectiveness and toxicity. An allergic patient, following complete study, may be tried on one or another of the drugs to determine their efficacy and the minimum of undesirable side reactions. Our observations indicate that Benadryl is the most potent antihistamine compound in relieving clinical bronchospasm, but it causes uncomfortable and often serious side effects in over 50 per cent of patients. Pyribenzamine, on the other hand, can compare favorably with Benadryl in most allergic disorders except asthma and causes less distressing and only half as many side reactions. Anthallan was found to possess very weak antihistamine properties, if any at all, but was very valuable particularly in treating skin disorders having an allergic background. Its relative freedom from side effects is a major advantage. Seasonal and non-seasonal allergic rhinitis and vasomotor rhinitis could be handled effectively with either Benadryl or Pyribenzamine, the latter offering more cures.

Bronchial asthma was the allergic disorder most resistant to all three drugs. Benadryl was found to be the most efficacious of the three in this condition but gave partial relief in only 25 to 50 per cent of patients. Anthallan offered considerable relief to hay-fever patients in particular but had a higher percentage of failures than the other drugs. Atopic dermatitis, acute and chronic urticaria, and angioneurotic edema may be considered to be effectively treated with the three drugs, but a larger series of patients is preferred for final judgment. Peculiarly enough, using Anthallan in large doses over a long period of time caused an apparent cure in the allergic skin disorders inasmuch as no relapses were noted in the patients studied. Vasomotor rhinitis was treated with reasonable success with the three drugs. It may be advisable to give each drug a trial test in this condition.

In a good number of cases it was considered that the ideal treatment of the allergic disorder was perennial desensitization with the allergen, together

with concurrent use of the antihistamine drugs. At present, however, their value still appears to be the temporary relief of various allergic symptoms. If infection plays a leading part in the disorder, eradication of the infective focus is considered mandatory. On the whole, it is too early to give a complete estimate of Benadryl, Pyribenzamine, and Anthallan in counteracting allergic symptoms. Their long-range effectiveness, tolerance, and clinical limits are still unanswered questions. Final judgment must be reserved until future studies are completed.

Conclusions

1. Benadryl, Pyribenzamine, and Anthallan are effective agents in treating many allergic disorders, presumably by neutralizing the effects of histamine.

2. The drugs are not a panacea and offer only palliative treatment. Anthallan, however, in a great many cases has produced an apparently permanent cure.

3. Benadryl has been found to be the most potent drug of the series in the treatment of seasonal and perennial allergic rhinitis, vasomotor rhinitis, bronchial asthma, urticaria, angioneurotic edema, and atopic dermatitis. It causes, however, a large number of undesirable side reactions which may endanger the welfare of the patient.

4. Pyribenzamine has been found effective in treating the above allergic disorders, though possessing less potency than Benadryl. It possesses a chief advantage of causing only half as many side reactions as Benadryl.

5. Anthallan is a weak antihistamine agent and has been found effective in treating allergic rhinitis and vasomotor rhinitis. Its outstanding quality appears to be the prevention of relapses in acute and chronic urticaria, angioneurotic edema, atopic dermatitis, and infantile eczema. No toxic side effect was encountered.

6. In accordance with other investigators this study reveals somnolence, fatigability, dry mouth, dizziness, urinary frequency, nervousness, and epigastric discomfort as the chief side reactions of Benadryl and Pyribenzamine.

7. There is no substitute for an adequate investigation into the allergic problem, and the antihistamine drugs should not be used until the exact nature of the problem is ascertained.

8. Concomitant therapy may be effectively administered.

9. Indiscriminate use of Benadryl, Pyribenzamine, and Anthallan should be discouraged because of the severe side reactions encountered, particularly with Benadryl and Pyribenzamine.

10. Future studies must be carried out before the definitive place in therapy of Benadryl, Pyribenzamine, and Anthallan can be appraised.

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THE THERAPEUTIC USE OF RADIOACTIVE ELEMENTS IN MALIGNANCY *

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DURING the past year there have been numerous allusions to the rôle to be played in medicine by the developments in atomic fission. The uninitiated reader might infer that such applications are something solely to be looked for in the future, contingent on a considerable amount of developmental research. There is no need to argue the need for fundamental investigation in this field. The need will always exist regardless of our progress. However, for the better part of 10 years, methods and tools of nuclear physics have been applied to medicine. In general, this application has been in two directions. First, isotopes offer much promise in solving the mysteries of metabolic processes in the animal and human body. Second, the artificially produced radioactive isotopes have opened up such broad horizons in the treatment of malignant disease that they will ultimately in all likelihood far surpass x-ray and radium together in therapy.

The metabolic use of isotopes and their diagnostic applications embrace such wide fields in physiology, biochemistry, medicine, surgery and biology that volumes could be written about the progress which has been made in the past decade. Probably no single new tool has had such a far-reaching influence on medical science or caused more concepts to be altered.

Comparatively little attention has been paid to the numerous possibilities for research in the therapeutic use of isotopes. It is with this field that we shall deal in this communication.

Up to recent months the chief and nearly sole source of isotopes was the cyclotron. As a result relatively few clinical investigators had access to artificial radioactive material for study. Due to the limited supply, attention was directed largely to the use of a few of the most available cyclotron produced isotopes. Radioactive phosphorus is one of these and has been employed in the treatment of a variety of diseases. The chain reacting uranium pile now presents a new and prodigious source of isotopes.

Below we list what appear to us to be the criteria for therapeutic usefulness of radioactive isotopes:

1. The "half-life" must not be too long. Neither should there be an associated component of long half-life or a long-lived contaminant whose separation is difficult or impossible to effect. Such long-lived materials prevent good control of the supplied radiation and also might prove ultimately

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to be carcinogenic in themselves. We have arbitrarily set about 10 days as the upper limit of half-life which is desirable from this point of view.

2. The half-life must be sufficiently long that the isotope can perform its work. This is important also since it is generally felt that the continuous delivery of radiation has advantages over delivery of a short burst of more intense radiation. Lower limits of half-life must for the present be dictated by shipping facilities and we have felt that two days represents the minimum at this time unless one is very near the source of material. Later it may be possible to use some of the isotopes with shorter half-lives to great advantage and this restriction is therefore purely temporary. However, as shorter half lives are used increasingly high activities are required for a given effect thus presenting technical problems in the maintenance of radiation safety for the operator.

3. The biological behavior of the material to be used should be well established since its effectiveness from a standpoint of localization is involved.

4. The chemistry of the element to be used must be well understood. Isotopes of some of the rarer elements which are now difficult to obtain in pure form with convenience may later have practical value.

5. The radiation spectrum of the isotope should be established and proper cognizance of the relative beta and gamma radiation which it is desired to deliver to tissue taken into account. If a hard gamma ray is emitted, proper shielding in shipment and in the laboratory becomes more difficult.

6. The radioactive material should preferentially be deposited selectively in the tissues it is desired to treat.

7. If the isotope is toxic, specific activity becomes important in keeping the dosage of material well under toxic limits.

8. The cost of producing and shipping the isotope is of great importance and will take on added significance as the use of isotopes in therapy becomes more widespread.

In table 1 are listed a number of isotopes culled from Seaborg's table [1] which lists some 450 known radioactive isotopes. The list in table 1 was made with several objects in mind. In general the criteria discussed above were considered to be limiting factors. In several instances isotopes were listed in order to point out how most of the criteria could be satisfied but one or more of these might limit the use of that particular isotope either now or perhaps forever. The most striking observation is the paucity of isotopes which hold promise of use as therapeutic agents. There are only about a half dozen which deserve critical investigation and appraisal at this time. Later the list may be increased slightly in length as it becomes feasible to utilize some of the shorter lived materials.

Let us consider the advantages and disadvantages of this small group in some detail. In the treatment of certain diseases the radiological therapist has found that "spray radiation," i.e. generalized x-radiation over the whole body is of value. Under such conditions a comparatively long continued low grade radiation might have advantages over a short exposure to a more

TABLE I

Isotope	½ Life	Long-Lived Contaminants	Specific Activity*	Chemical Knowledge*	Knowledge of Biological Behavior*	Radiation	Yield	Comment
Na^{24}	14.8 hr.	None	B	A	A	Hard β^- and γ	A	Very heavy lead protection required
P^{32}	14.3 d.	None	A	A	A	β^- only	A	Half-life slightly too great
K^{42}	12.4 hr.	None	C	A	A	Very hard β^-	A	Of doubtful present biological use
Mn^{52}	6.5 d.	Mn^{54}	A	A	B	β^+, K and hard γ	A	Long-lived contaminant, heavy lead protection
Cu^{64}	12.8 hr.	None	B	A	B	β^-, β^+, K, no γ	A	Use limited by short half-life
Ga^{72}	14.1 hr.	None	C	B	D	Hard β^- and γ	B	Not therapeutically promising
As^{76}	26.8 hr.	None	C	A	B	Very hard β^- and γ	B	Low specific activity for toxic element
Br^{82}	34 hr.	None	C	A	B	Medium β^- and γ	B	Half-life rather short
$Kr^{79,81}$	34 hr.	None	C	A	B	β^+ only	C	A radioactive inert gas
Y^{90}	60 hr.	None	C	B	C	Very hard β^- only	B	Further biological study required
Mo^{99}	67 hr.	None	C	A	C	Hard β^-, medium γ	B	Further biological study required
Ag^{111}	7.5 d.	None	A	A	B	β^- only	B	A promising pure β ray emitter
I^{130}	12.6 hr.	None	A	A	A	Medium β^- and γ	A	A good cyclotron isotope for therapy
I^{131}	8.0 d.	None	A	A	A	Medium β^- and γ	A	A good pile isotope for therapy
La^{140}	40.0 hr.	None	B	C	D	Hard β^- and γ	B	Further biological study required
Au^{198}	2.7 d.	None	A	A	B	Medium β^- and γ	A	A good therapeutic isotope
Au^{199}	3.3 d.	None	A	A	B	Medium β^- and γ	B	Very high specific activity possible
Bi^{207}	6.4 d.	None	A	A	B	Medium γ, K?	B	Production limited to cyclotron yield

* The classification is as follows: A—good; B—fair; C—poor; D—very poor.

intense source of radiation because of the suspected increased susceptibility of cells during mitosis. Actually such a feature of relatively constant low grade radiation, which presents practical economic difficulties to those using x-ray, is one of the chief advantages which isotope therapy has to offer. Sodium in ionizable form is uniformly distributed in the extra-cellular water of the body some hours following the administration of NaCl orally or by vein.[2] Evans and Quimby [3] have compared the effects of "spray radiation" by means of x-rays with that obtained by the use of NaCl in mice and have found that the results were similar. The chief advantage in the use of Na^{24} isotope here would be the possibility of extending the radiation period for many hours. On the debit side is the difficulty of shipping and handling the sodium isotope because of the exceptionally hard gamma ray emitted.

A great deal has been written concerning the use of P^{32} as a therapeutic agent and this has best been summarized by the report of Reinhard, Moore, Bierbaum, and Moore.[4] They conclude that success in its use has been most conspicuous in the treatment of polycythemia vera and possibly in myelo-

genous leukemia. We have already expressed ourselves as being not in favor of use of isotopes in treatment of polycythemia except under unusual conditions since phlebotomy is much simpler, without hazard to the patient, and quicker in its action.[5] If the usefulness of P^{32} in treatment of myelogenous leukemia is due to the semi-specific action on the bone marrow it seems reasonable to expect that one of the other isotopes discussed below might be more advantageously employed. We also feel that the half-life is too long, making a "titration" of the administered radiation difficult. It would seem that the widespread use of P^{32} has been based largely on its availability as a cyclotron product, and that it should soon have competitors under the new pile economics.

Use of manganese (Mn^{52}) would be feasible if only a single or several treatments were necessary since then the inclusion of about 1 per cent of the long-lived accompanying component (Mn^{54}) would be relatively unimportant. However, experience [6, 7] has shown that patients with malignancies of the lymphoid system usually require repeated treatment and it must therefore not be included in the armamentarium of isotopes useful for such therapy.

Cu^{64} is a good example of an isotope which may at some time in the future offer possibilities in therapy. It is an element closely associated with certain enzyme systems and is somewhat selectively taken up by certain tissues. However, its short half-life precludes its widespread successful use at this time due to difficulties in shipping and prompt use.

As^{74} presents an example of a debatable element for inclusion in a list of therapeutic agents. Because of its toxicity the low specific activity is against its use. However it possesses some degree of selectivity in deposition in tissues; large amounts are commonly administered in anti-syphilitic therapy; all in all more study should be devoted to its possibilities before condemning it.

$Yttrium^{90}$ differs from its neighbor strontium only in possessing a single 4d electron in an interior N shell and thus has similar chemical properties. It should be studied to see if it behaves similarly to strontium in replacing some of the body's metabolic calcium. Its hard pure beta particle spectrum should make it an exceedingly useful substitute for P^{32} or long lived strontium in the treatment of diseases of the bone and marrow such as myelogenous leukemia, Ewing's tumor, and bone sarcomata.

Ag^{111} has not yet been tried, but affords room for much speculation as a possible material for use topically or by direct injection because of its propensity to attach itself to protein and remain in situ. It is a pure beta emitter and its radiation would be well localized.

I^{130} and I^{131} have been investigated fairly thoroughly and will probably play an increasing rôle in handling of certain diseases of the thyroid. It is representative of superb biological selection which is an aim to be set for the use of most isotopes.

Au^{198} has only recently been tried as a therapeutic agent [8, 9, 10] and it is too early to determine its full value or future in therapeutic use. It has many

of the desirable characteristics and was selected as having the most promise from a standpoint of satisfying the criteria delineated above. In addition it is easily made in pure form without any trace of discernible contaminant isotope. Its chemistry is unique and well understood. Its insolubility as a metal allows it to be injected with reasonable assurance that it will stay at the site of injection, when given subcutaneously or intramuscularly. It is not subject to excretion when administered as the metal and therefore does not give rise to problems of radioactive excreta or loss from the body with accompanying lowered efficiency and uncertainty as to dosage. Theoretically it should be more useful than radium in local radiation of tissues since it can be infiltrated throughout the affected area. Thus it is not necessary to establish highly local sites of intense radiation with concomitant lack of radiation to adjacent areas not accessible to direct radium application. Furthermore, it is not necessary to remove the material injected thus allowing infiltration freely during operative procedures.

We now turn from a consideration of possible isotopes to an outline of a few suggested technics in therapeutic use. Some of these have received preliminary study but a number have not yet been tried and certainly bear investigation.

I. For general body radiation to correspond to spray x-radiation.[3]
   1. Na^{24} has been used for this purpose since it is generally distributed in the total body water.

II. Utilization of the peculiar affinity of a tissue for a given isotope in order to obtain localized radiation.
   1. $I^{130, 131}$ and its use in therapy of hyperthyroidism and thyroid tumors.[10, 11, 12]

III. Utilization of chemical affinity of tissue for an element and substitution of another element which behaves similarly physiologically but has a more suitable spectrum, half-life or other characteristic, or which is more readily available.
   1. Sr^{85} as a substitute for calcium, there being no suitable Ca isotope for therapy of metastatic bone tumors.[13] Its disadvantage is the 55 day half-life. Yt^{90} may be found to provide an even better substitute. However, its biological distribution must first be studied.

IV. Utilization of the semi-specific uptake of elements by tissues where some degree of generalized radiation is either desirable or not strongly contraindicated.
   1. P^{32} in therapy of myelogenous leukemia and polycythema vera.[4]

V. Utilization of specific functions of certain tissues in their physicochemical behavior toward administered materials.
   1. Phagocytosis of intravenously administered particulate material in concentrating radiation in the reticulo-endothelial system. Radioactive particles of gold, manganese dioxide, and chromic phosphate have been used for selective radiation of this system,

especially the liver and spleen, in the leukemias, Hodgkin's disease, lymphoma, and other disorders.[6, 8, 14]

2a. Intraperitoneal injection of colloidal material for removal by abdominal lymph nodes in diseases such as lymphoma and abdominal Hodgkin's.[16]

2b. Intrathoracic injection of colloidal material for removal by mediastinal and hilar nodes in pulmonary tumors and metastatic involvement of the thorax.

3. Utilization of chemo-tactic properties of the system to obtain localization, e.g. at the site of inflammatory processes. The behavior of certain dyes in this respect suggests the use of attached isotopes.

VI. Topical application of isotopic material in therapy of superficial lesions.

1. Preliminary studies using P^{32} as reported by Low Beer.[15]

2. Preliminary studies using colloidal Au^{198} and $Ag^{111}NO_3$.[16]

VII. Treatment of tumors of the hollow viscera by instillation of radioactive materials to obtain radiation by proximity.

1. Therapy of bladder tumors by instillation of suspension of radioactive material in non-absorbable form, e.g. colloidal Au^{198}.

1a. Instillation of material which would readily bind itself to mucosal surface affording localization to a higher degree, e.g. $Ag^{111}NO_3$.[16]

2. Instillation of jelly containing isotopic material in uterine cervical tumors.

3. Retention enema therapy of carcinoma of rectum or colon.

4. Localized radiation of the involved area in carcinoma of stomach.

a. Use of the double lumen Miller-Abbott tube to plug the pylorus. Installation of a short-lived isotope in insoluble form. Adjustment of position of patient under the fluoroscope in order to cause pooling at the desired site. Withdrawal and rinsing of the solution from the stomach at desired time.

5. Localized radiation of selected segments of the intestinal tract.

a. Use of the three lumen Miller-Abbott tube with distal and proximal balloons. Suspended material in unabsorbable form is mixed with a small amount of barium and introduced into the third lumen to fill the interspace. It is then pumped and rinsed after a desired interval of time.

VIII. Selective therapy of specific organs or tissues making use of specific action of certain drugs to manipulate the progress of the isotopic material.

1. Radiation of the spleen alone or at least with minimal radiation of other parts of the lymphoid system. The subject is nembutalized to cause engorgement of the spleen and its temporary physiological removal from the phagocytic system. Injection of a moderately large, semi-blocking dose of non-radioactive colloidal material, such as Trypan blue, or colloidal carbon. Administration of a small amount of epinephrine to contract the spleen. Administration of

colloidal radioactive preparation by vein for phagocytosis by the spleen.

IX. Therapy of pulmonary carcinoma by direct inhalation of radioactive material.
   1. Use of an isotope prepared as an aerosol.
   2. Direct use of a radioactive gas such as Krypton.
   It is difficult to evaluate either of these procedures until further studies have been made.

X. Direct radiation of discrete masses of tumor tissue by infiltration of the tumor with an inert, insoluble isotopic material such as Au^{198} or Ag^{111}.[16]

XI. Physical manipulation in localization of the distribution of radioactive material.
   1. In the therapy of leukemia one of the limiting factors in the administration of sufficient radiation therapy with isotopes is the possibility of induction of leukopenia and thrombocytopenia by irradiation of the bone marrow. This might be partially avoided by occluding the circulation to the extremities prior to the intravenous administration of material to be removed from the circulation (see V. 1). Since disappearance from the circulation is very rapid the blood stream should be satisfactorily cleared of the therapeutic material within a short time and circulation might then be restored. In this way the marrow of the long bones may be available to furnish leukocytes and platelets during the period when maximum cellular destruction of the other marrow was taking place. When the marrow of the head and trunk had recovered its ability to produce cellular elements, the long bones could be treated by x-ray.

We do not wish to suggest that all of the possibilities which we have listed above are well enough established to justify their immediate use. Some of the technics have been given clinical trial and have shown themselves to be feasible. Others offer sufficient promise that they might shortly be applied in medicine with little additional developmental research. A few are sufficiently controversial that they require considerable additional analysis. Experience has shown that during the investigation of the feasibility of methods of radiation therapy enough basic information is usually obtained to justify the effort even when a negative result is encountered.

Some may argue that we are not prepared to begin the therapeutic use of isotopes on a large scale until more is known concerning the unfavorable side reactions produced by radiation and the possible untoward end results which might accrue from their use. It is true that there should be no indiscriminate use of these materials. They must be placed in cautious and competent hands. Furthermore one must be hesitant to use radiation in any form in the treatment of any disease which runs a benign course. However, there

is every reason to proceed with vigor in attacking those malignant conditions in which the prognosis is poor even though our knowledge is incomplete at the moment. If we were to wait 10 more years on the assumption that the necessary fundamental background could be built up in that time, there would have been many hundred thousands more victims of malignancy who might have been helped to some degree, barring some revolutionary new form of therapeutic approach to this problem not in sight at this time. If the outlook for continued life in such a disease is but a few months, one is perfectly justified in taking some risk in treatment when there is every reason to believe that a certain percentage of the patients may obtain some relief and some may have many years added to their lives.

The fiftieth anniversary of the use of roentgen-rays has recently been celebrated. Certainly in the first 30 years of their use, many mistakes were made. The hazard involved in the use of this tool, however, did not preclude its widespread application in the treatment of malignant disease. It should not be said that with the wider range of radiation spectra available and the resultant increased complexity of the underlying problems facing us, we should hesitate to embark on the productive use of these extremely valuable and now available agents. Their flexibility suggests a multitude of uses. It is to be hoped that they will be used widely but wisely.

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THE INHALATION OF DUST PENICILLIN *

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In view of the favorable reports in recent literature on the inhalation of therapeutic agents, especially penicillin, and because of the many possibilities of the method, we have attempted to produce even greater and more protracted topical effectiveness by a method which involves the inhalation of fine dust aerosol particles. This method has simplified the mechanics of aerosol therapy, thus expanding its scope more readily for office and home treatment.

Aerosols may be defined as suspensions of liquids or solids in air or oxygen. In the past, the aerosolization methods have included only the inhalation of suspensions of liquids. The method described in this paper will be referred to as the inhalation of dry dust penicillin, thus distinguishing it from the former penicillin vapor method.

The apparatus used for inhalation therapy in the past has been based on the delivery of the aerosol vapor under positive pressure of oxygen or air by means of a hand bulb, oxygen tank and gauge, or compressed air machine. The principle utilized in the new method is based on the negative pressure created by normal breathing during the inspiratory phase. Inhaling penicillin dust in this manner is more physiological and permits an even, and perhaps a wider distribution of medicament throughout the respiratory tract. The patient is not required to manipulate an exhaling valve during the expiration phase, and the cumbersome equipment of oxygen tank and gauge is unnecessary. The inhalation of the dust particles of penicillin yields greater effect than the vapor because there is greater concentration of penicillin per unit area and because the penicillin must go into solution while in contact with the mucous membrane before it can be absorbed.

The penicillin dust used in this experimental study was Crystalline Sodium Penicillin, processed to number 100 mesh particles.† The crystalline form was found to be less hydroscopic than the amorphous sodium penicillin salt and could be stored at room temperature without losing its potency more readily than the penicillin liquid, which is used as the nebulin for the vapor method.

There were a number of objectives which this study attempted to achieve. They were: 1. To determine whether penicillin as a fine dust has any irritating qualities or will give rise to untoward effects when inhaled. 2. To develop a simple and efficient practical device for the inhalation of penicillin

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† The penicillin for this study was especially processed by, and furnished through the courtesy of Abbott Laboratories, North Chicago, Illinois.

dust, which would lend itself to home and office use. 3. To determine the effectiveness of this method upon the bacterial contents of the nose, throat and sputum in patients with varying types of respiratory infections. 4. To determine the rate and degree of absorption of the medicament into the systemic circulation. 5. To evaluate the effectiveness of the method as compared with the vapor aerosol inhalation method and other known routes of penicillin administration.

Apparatus

The apparatus was designed in terms of the aforementioned objectives, namely,

1. To deliver penicillin as a fine, nonirritating dust to respiratory tract.
2. To have a simple, efficient and practical mechanical device for use at home, in the office, and in the hospital.

The apparatus now being used represents numerous modifications of the original device * since penicillin dust possesses certain qualities which do not lend themselves to ordinary technics. Penicillin is highly electrostatic, easily adhering to surface areas. In addition, it is hydroscopic and goes into solu-

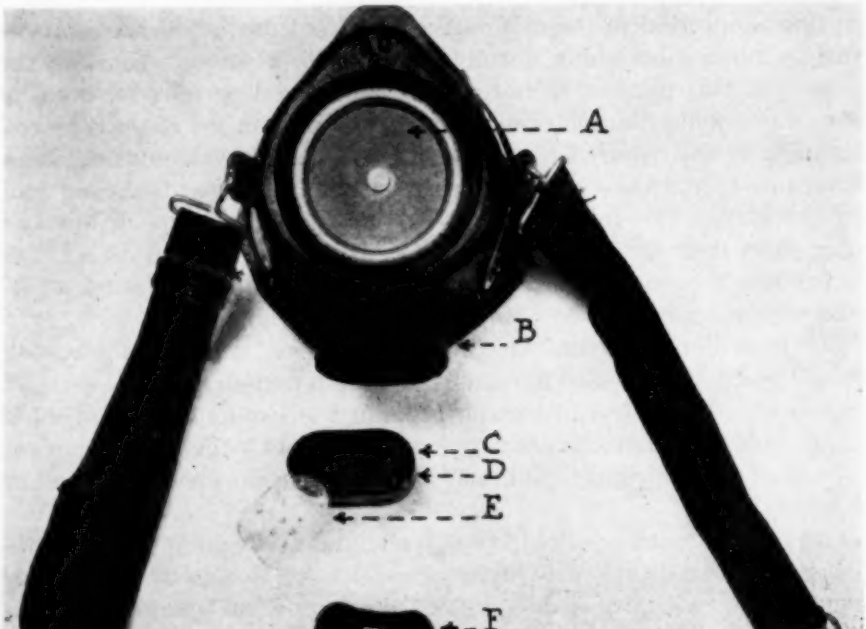


Fig. 1. Mask used for the inhalation of dust penicillin.

* The present mask was kindly fabricated by the Chicago Eye Shield Company, according to the specifications of one of the authors (Krasno).

tion readily. The technic finally developed allows the penicillin to be released easily as a dust and at the same time precludes the moisture of exhalation from dissolving it.

The device consists of an oro-nasal face piece which is held on the face by an elastic head band (figures 1 and 2). The front of the mask contains a

FIG. 2. Mask assembled and applied to patient's face.

large exhalation valve (A) in direct line with the stream of exhaled air. The portion of the mask about the chin contains a rubber sleeve (C) fitted with an inhalation valve (B) which directs the inhaled air in the plane at right angles to the stream of exhaled air. The inhalation valve contains a special detachable metal chamber (D) containing the penicillin dust. The penicillin chamber is fixed with a fine wire mesh (E) which is covered with a finely perforated cellophane paper (F). It has been found that penicillin dust is essentially non-adherent to cellophane. The penicillin dust is placed on top of this platform. During the inhalation, air is drawn through the per-

forations of the penicillin chamber and the dust is released, passing through the inhalation valve and into the respiratory passages. The penicillin dust is protected from the moisture of exhalation by the one-way inhalation valve and by the fact that the exhaled air is conducted through a plane at right angles to the inhaled air. There is a small hole (H) about 6 mm. in diameter on top of the mask just above the end of the nose. This allows a substantial amount of air to be drawn in easily and avoids any resistance on inspiration. This supplementary inlet for air is also necessary to keep the amount of penicillin dust inhaled in optimum quantities.

Experimental Procedure

Sixty-six subjects, 36 males and 30 females, were used in this experiment.* The age variation was from 7 to 72 years. The subjects were divided into three groups. The first group consisted of four experimental subjects (including the authors) on whom any irritating properties or untoward effects of inhaling penicillin dust would be detected. The second group comprised 23 patients who were hospitalized for various types of respiratory diseases. The third group consisted of 39 ambulatory patients who came to the office or hospital for penicillin treatment.

Throat, nose and sputum cultures were obtained on the experimental subjects prior to the inhalation of 100,000 or 200,000 units of penicillin and at one and two hours following inhalation. Blood levels were obtained on various subjects in this group. All hospitalized patients received 100,000 units of penicillin dust by inhalation for 20 minutes three times a day. All treatments followed meals to reduce the possibility of washing down the penicillin from the pharynx into the stomach. Throat and nose cultures prior to first treatment and daily cultures thereafter were taken on all hospitalized patients. Preliminary and follow-up sputum cultures were obtained in all cases of bronchiectasis. Blood levels were made on various patients. The clinical progress was followed by the patient's doctor and the authors. The duration of therapy was determined clinically and bacteriologically for each case.

The majority of the office patients were given one treatment of 100,000 units of penicillin, an occasional patient receiving more than one treatment. The symptoms, duration of symptoms and physical findings were noted prior to inhalation, and 24 hours after the treatment was given. It was not practical to obtain cultures on this group, but the data accumulated from these office patients served to give further information regarding the course of symptoms and allergic aspects as influenced by this type of treatment.

Results

Table 1 lists the type of pathological conditions for which these patients were treated. The greater portion had upper respiratory tract infections,

* The observations reported here cover a period extending from October 1946 to February 1947 inclusive. The results obtained since that time are essentially the same as reported

TABLE I

Clinical Diagnosis of Cases Treated

Clinical Diagnosis	No. of Cases
I. Upper respiratory infections	
a. Common cold (acute rhinitis and/or acute nasopharyngitis)	46
b. Chronic nasopharyngitis	4
c. Chronic sinusitis	3
d. Laryngotracheal bronchitis	2
II. Lower respiratory infections	
a. Bronchiectasis	6
b. Chronic bronchitis	2
c. Bronchial asthma with chronic bronchitis	1

TABLE II

Summary of Bacteriological Data: Throat Cultures

Organism	Pre-therapy Growth			Post-therapy Growth			No Growth
	Heavy	Moderate	Slight	Heavy	Moderate	Slight	
1. α hemolyticus streptococci (*Str. viridans*)	17	12	1	1	4	9	16
2. β hemolyticus streptococci (*St. hemolyticus*)							
3. Diplococcus pneumococci	1	10					11
4. γ streptococcus anhemolyticus		4			2		2
5. *Staphylococcus aureus*	1	10	3		7	3	4
6. *Staphylococcus hemolyticus aureus*	1	4					5
7. *Staphylococcus albus*	5	17	2		10	4	10
8. *Neisseria catarrhalis*		11	2		6	4	3
9. *Micrococcus tetragenous*		3					3
10. *Aerobacter aerogenes*		1				1	0
11. *B. hoffmannii*		3				1	2
12. Diphtheroids		2				1	1

Numerical values represent number of cases.

TABLE III

Summary of Bacteriological Data: Nose Cultures

Organism	Pre-therapy Growth			Post-therapy Growth			No Growth
	Heavy	Moderate	Slight	Heavy	Moderate	Slight	
1. α hemolyticus streptococci		2					2
2. β hemolyticus streptococci		1					1
3. Diplococcus pneumococci							1
4. γ streptococcus anhemolyticus		1					1
5. *Staphylococcus aureus*		2					2
6. *Staphylococcus aureus hemolyticus*		3				1	
7. *Staphylococcus albus*		7	4		1	2	8
8. *Neisseria catarrhalis*		1	1				2
9. *B. proteus vulgaris*		1					1

Numerical values represent number of cases.

39 of which had symptoms of the "common cold," such as acute rhinitis, lacrymation, nasopharyngitis and general malaise.

It can be seen from tables 2, 3, and 4 that the inhalation of dry penicillin quickly causes the reduction or disappearance of gram positive bacteria and

in the massive doses used seems to influence some of the gram negative bacteria. This is accomplished readily, often in one treatment. Penicillinase has been added to the laboratory specimens without changing the bacteriological results.

Bacteriological Data on Throat Cultures

Table 2 illustrates the effect of dry penicillin therapy on the various types of organisms found in the throat. The table is arranged according to the extent of the growth of a given organism before and after course of therapy. It is interesting to note that all of the organisms, including the gram negative

Table IV

Summary of Bacteriological Data: Sputum Cultures

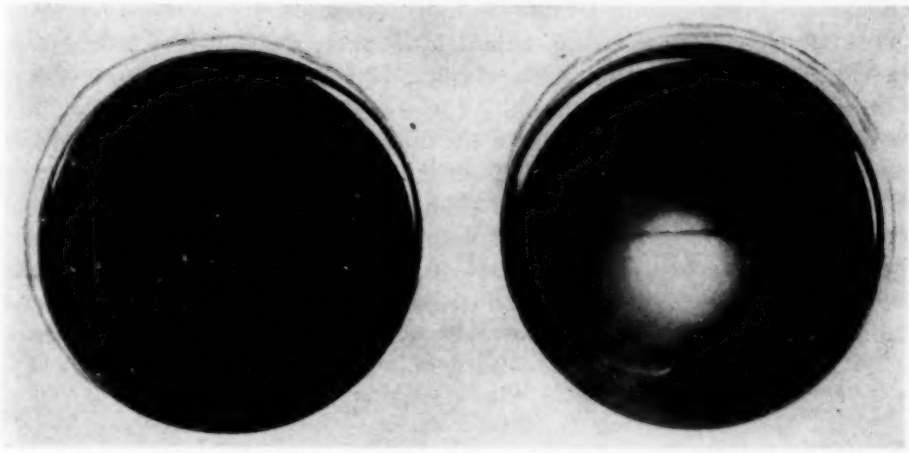
Organism	Pre-therapy Growth			Post-therapy Growth			No Growth
	Heavy	Moderate	Slight	Heavy	Moderate	Slight	
1. α hemolyticus streptococci (*S. viridans*)	6	5				4	7
2. β hemolyticus streptococci		2					2
3. Diplococcus pneumococci		1	2				3
4. γ streptococcus anhemolyticus		2			1		1
5. *Staphylococcus aureus*	3	3			2	2	2
6. *Staphylococcus albus*	1	5			5		1
7. *Neisseria catarrhalis*		3	1		2	2	
8. *Micrococcus tetragenus*		1					1
9. *B. mucosus capsulatus*		2					2
10. *Neisseria pharyngis sicca*			1				1

Numerical values represent number of cases.

bacteria, were appreciably influenced by the treatment. Prior to inhalation of penicillin dust 14 patients had a heavy growth of *Streptococcus viridans*, 10 showed a moderate growth, and one had a slight growth. After a course of treatment, there was one instance of heavy growth, four of moderate growth, seven showing slight growth, and 13 with no growth evidenced after 72 hours of incubation on blood agar plates. In the cases with *D. pneumoniae*, there was one of heavy growth, 10 with moderate growth before inhalation of dry penicillin. After therapy the *D. pneumoniae* disappeared in all 11 patients.

Bacteriological Data on Sputum Culture

Table 4 illustrates the effects of the treatment on the sputum specimens. Before therapy six cases showed a heavy growth of *Streptococcus viridans*, and five a moderate growth. After inhalation of dry penicillin there was a slight growth in four and no growth in seven cases, one patient exhibited a moderate growth of *D. pneumoniae* and two a slight growth, which disappeared in each instance following therapy. In two cases there was a mod-



A B

FIG. 3. Blood agar plates. (a) demonstrates growth of bacteria from throat culture before inhalation treatment and shows heavy growth of small colonies producing green hemolysis (*Streptococcus viridans*). (b) Blood agar plate of throat culture taken two hours after inhalation of 100,000 units of penicillin. Reported no growth 72 hours.

erate growth of *Streptococcus hemolyticus* which completely disappeared after inhalation treatment.

CLINICAL EVOLUTION OF RESPONSE TO DRY PENICILLIN THERAPY

Table 5 represents the symptomatic improvement of the 39 patients treated at the hospital as judged by the patient himself, the attending doctor and the authors. Ten cases were rated a two plus improvement, 15 a three plus improvement, and 14 a four plus improvement.

A study of the data on six bronchiectatic patients revealed less cough and secretion in these patients on dismissal. The patient with bronchial asthma

TABLE V

Results in the 23 Hospital Patients

Clinical Diagnosis of Cases	Clinical Results			
	+	++	+++	++++
I. Upper respiratory infections				
a. Common cold (acute rhinitis and/or nasopharyngitis)		3	8	10
b. Chronic nasopharyngitis		1	2	1
c. Chronic sinusitis		2	1	
d. Laryngotracheal bronchitis				2
II. Lower respiratory infections				
a. Bronchiectasis		3	3	
b. Chronic bronchitis		2		
c. Bronchial asthma with chronic bronchitis			1	

Clinical results expressed in one, two, three or four +.
Numerical values represent number of cases.

and chronic bronchitis had marked improvement, the infectious condition almost completely disappearing, although the allergy persisted to a decreased degree. The two patients with chronic bronchitis showed a moderate improvement.

It was in the acute conditions of the upper respiratory tract that the best results were obtained. Over 90 per cent of the 23 patients with upper respiratory tract infections treated at the hospital had marked improvement in their symptoms. Those patients with acute rhinitis and laryngo-tracheo bronchitis had recovered within one to three days. "The common cold syndrome" of acute rhinitis, lacrimation, naso-pharyngitis, and general malaise responded to the inhalation therapy; eight cases were listed as three

TABLE VI

Office Patients

Patients	Cough	Fever	Rhinitis	Sore Throat	Chest Pain	Earache	Headache	Malaise	Duration of Symptoms				Number of Treatments	Response to Treatments
									Days	Wks.	Mos.	Yrs.		
1	+			+			+	+		3			1	+++
2**	+		+	+					2				1	+
3	+		+	+			+	+		1			1	++
4	+		+	+							1		1	++++
5	+		+	+						3			1	++++
6	+		+	+	+		+	+	5				1	++++
7*	+						+	+				14	1 per week	+++
8	+		+	+			+	+	6				1	++++
9	+	+	+	+				+	5				1	++++
10**				+		+	+	+	3				1	+
11	+	+	+	+			+	1	4				1	++++
12	+	+	+		+		+			1			1	+
13	+			+	+					1			1	++
14	+		+	+					5				1	++++
15	+		+	+			+	+	4				1	+++
16	+		+				+	+		1			1	++
17*	+											10	1 per week	+++
18	+											4	1 per week	++
19	+		+	+					4				1	++++
20	+	+	+	+	+				3				1	+++
21	+				+							1	1 per week	++
22							+					5	1 per week	+++
23	+				+							3	1 per week	+++
24**	+		+	+					2				1	++
25	+		+	+					10				1	++++

* Ambulatory bronchiectatic patients.

** In these cases, the immediate response was minimal but the patient felt much better 2 to 3 days thereafter.

plus improvement and 10 as four plus or complete improvement. Three had moderate or two plus elimination of symptoms.

Twenty-nine of 39 cases treated at the hospital (75 per cent) had only one treatment, six had two inhalations, and three had four treatments. The remainder had four to 18 inhalations, the highest number being reserved for the chronic bronchitis and chronic sinusitis patients. The patients with

diseases of the lower respiratory tract had from 10 to 18 treatments, administered in four to six days.

It is singular that to the present time and including 66 cases there has been noted no sensitivity reaction to the penicillin. With the vapor aerosol method, transient fever, dyspnea or dermatitis has occurred in 4 to 20 per cent of the cases, depending upon the concentration of the drug used.*

Table 6 lists the duration of symptoms prior to the treatment and degree of improvement within 24 hours in a group of office patients treated with dry penicillin.

Penicillin assays of urine and blood were determined by Fleming's modification of the Wright slide cell technic.[1] Defibrinated sheep blood was used instead of human blood and the results were read directly from the test tubes without the use of slides. Single blood determinations were made on patients in the hospital and penicillin blood curves were established.

Table 7 illustrates the results of the penicillin assays of the blood and shows values from .03 to 1.92 units per cubic centimeter. Blood level curves would indicate a slow absorption, the maximum level being obtained 3 to 3½ hours after the inhalation.

Comments

It is difficult to evaluate therapeutic results in a preliminary report. Records of clinical improvement as judged by patient and doctor have no more value here than in any other clinical study. However, we are in the process of running controls in the form of patients treated by other methods. The positive findings in the report are the definite, though perhaps temporary, changes in bacterial flora,† and the appreciable penicillin blood levels obtained. The duration of the change in bacterial flora has not been determined but the clinical improvement in many instances has been more than temporary. The clinical improvement is definite and further work is being carried out to investigate the duration of results. The main purpose of this preliminary report is to present a new method of administering penicillin. The method appears to offer more effectiveness in ridding the upper respiratory tract of gram positive bacteria than other aerosol methods. Appreciable blood levels would indicate the protracted, effective absorption offered by this method, and the possible use of inhalation treatment for systemic conditions other than those of the respiratory tract. This method would appear to have a definite value in initiating the process of ridding the respiratory tract of pathogens, but it may be necessary to supplement the process with intramuscular penicillin administration and with other medicaments. In other instances its value may be adjunctive rather than primary.

*Since the writing of this paper there has been one case of contact dermatitis allergy, manifested by an herpetiform-like rash in the skin area of nose and mouth. The dermatitis has reappeared in this patient on each attempt to repeat the penicillin inhalations.

† We wish to make it clear that pathologic significance is not attributed to all the bacteria listed in the tables, e.g. *Streptococcus viridans* in throat cultures.

TABLE VII

Penicillin Assays (Units per c.c. of Blood) from Blood Samples Drawn at Varying Intervals Following Inhalation Treatments

	Amount of Drug Inhaled	Age of Patient	Interval in Minutes											Interval in Hours			Misc.
			15′	30′	60′	90′	120′	150′	180′	210′	240′	270′	300′	420′	24 hrs.	30 hrs.	48 hrs.	
1	100,000 units	30	0	0	0	0	0	0	0	.24*	.24	.12	0					
2	200,000 units	54	.03			.06												
3	200,000 units	30			0		0		.03**	.03		0	0	.16			0	
4	100,000 units	28	.03		0		0		0	.06*	0		.06*			.03		urine assay = 30.72 u./c.c. after 2nd inhal.
5	100,000 units	2		1.92														
6	100,000 units	16	0	0	.06													
7	100,000 units	45							.48*	.12	.03	.48						

* Subsequent treatments of 100,000 units.
** Subsequent treatments of 200,000 units.

Conclusions

1. A method is presented for the administration of penicillin dust by inhalation.

2. The data given show that there is a marked diminution of gram positive bacteria of the upper respiratory tract following the treatments. Coincident with the treatment there is improvement in signs and symptoms of upper respiratory tract infections and bronchiectasis.

3. In many instances effective blood levels were demonstrated, usually, 3 to 3½ hours after inhalation.

4. The method appears to be more effective than other methods of inhalational penicillin therapy and causes fewer side reactions.

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SPONTANEOUS MEDIASTINAL EMPHYSEMA AND SPONTANEOUS PNEUMOTHORAX—A REPORT OF 20 CASES *

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THE rapidly increasing number of case reports indicates that spontaneous mediastinal emphysema is not rare.[1-12] Further case reports are essential to establish the frequency. The occurrence of spontaneous mediastinal emphysema, spontaneous pneumothorax and a combination of these two conditions among the students seen at the University of Wisconsin Student Health Service from March 1943 to March 1947 is reported for two reasons: first, because spontaneous pneumothorax is no longer considered a medical rarity and some estimations of its frequency have been recorded; second, and more important, to stress the frequency in which the two conditions are associated. In this way a clearer idea of the frequency of mediastinal emphysema may be gathered.

The actual incidence of spontaneous pneumothorax is difficult to establish, although numerous series have been reported.[13-16] In a recent report by Schneider and Reissman [18] the authors state that a verified history of spontaneous pneumothorax was given by about one in 500 men in a group of selectees in the 18 to 38 age group. Heath [19] reports 10 cases of spontaneous pneumothorax in a survey of 28,000 admissions to the A. A. F. Regional Hospital in Lincoln, Nebraska. These were all confirmed by roentgen study. Blackford [20] reports the incidence of spontaneous pneumothorax to be about one in 1000 among college students at the University of Virginia.

The usual explanation given for the production of spontaneous mediastinal emphysema is that the source of the air is from a ruptured alveolus or alveoli. From this site within the lung the air dissects along the perivascular sheath to the mediastinum. In Macklin's [21, 22] experiments with cats the associated pneumothorax was caused by a rupture of the mediastinal pleura with the resultant escape of air into the pleural spaces. The frequency of pneumothorax associated with mediastinal emphysema would indicate that this mechanism occurs in the majority of the spontaneous pneumothoraces seen in otherwise healthy individuals.[22] The reason for the overdistention and rupture of the alveolar wall in these patients is not understood. As a rule there is no history to suggest increased intrabronchial pressure immediately preceding the onset.

If this explanation be correct, then mediastinal emphysema should occur more frequently than spontaneous pneumothorax and the two conditions

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should be associated frequently. The failure to demonstrate free mediastinal air in a case of spontaneous pneumothorax by physical examination and roentgen study is not valid proof that the air escaped from a subpleural air collection instead of via the mediastinum. The evidence of mediastinal air may be transient or unrecognized. This is particularly true when a pneumothorax is found and regarded as adequate explanation of symptomatology. In either spontaneous pneumothorax or mediastinal emphysema the amount of air present may be too small or localized in such a manner that the diagnosis is not made although the history and course be so characteristic that this diagnosis seems probable. The difficulty of diagnosis is greater in the patient in whom the symptomatology is due to pulmonary interstitial emphysema, which in Macklin's [21] opinion is the precursor of pneumomediastinum and pneumothorax.

From March 15, 1943 to March 15, 1947 we have seen six students with spontaneous pneumothorax without recognized mediastinal emphysema, seven with pneumomediastinum without recognized pneumothorax, and seven in whom the two conditions were associated. Nine individuals with mediastinal emphysema with or without pneumothorax have been seen between January 1 and March 15, 1947. The university enrollment was approximately 18,000 during this period.

Only the 14 cases with mediastinal emphysema will be presented in the following case summaries:

Case 1. A 21 year old student was admitted to the infirmary March 23, 1943. While he was sitting in class he experienced a sharp pain in the precordium radiating through to his back. This pain was accompanied by mild dyspnea. As this patient had suffered from two previous spontaneous pneumothoraces he felt that he had a recurrence so came to the clinic immediately. During the initial examination he became faint. His skin was cool and moist and his pulse was thready. The only significant finding was a peculiar crepitus synchronous with the heart beat heard only at the pulmonic area at the height of full inspiration when the patient leaned forward. His pain disappeared in a few hours and the crepitus could no longer be demonstrated. No evidence of pneumothorax or pneumomediastinum was evident on fluoroscopic examination or chest roentgenogram. During the three day hospital stay he was afebrile. The sedimentation rate and white blood count were normal. A tuberculin test with 1.0 mg. O.T. remained negative. No electrocardiogram was taken. Subsequently this man was seen with recurrent pneumothoraces until after a total of three on the right and two on the left a bilateral chalk poudrage was done in August 1943. Recently he reported that he has had no further difficulty and considers himself to be in excellent health.

Case 2. On May 22, 1945 a 19 year old man noted the abrupt onset of pain in the substernal area radiating through to the back and occasionally to the left arm. The onset occurred while he was in class. His pain was increased by lying flat, by motion, and by breathing. Almost complete relief was obtained by lying on his right side. In January 1945 he had been hospitalized for a spontaneous right pneumothorax. On physical examination there were the usual signs of a left pneumothorax. Cardiac dullness was obliterated. Heart tones were distant and almost obliterated by loud crunching knocking sounds synchronous with the heart beat. The sounds disappeared if he turned on his right side. These signs of pneumomediastinum persisted for 10

days. Throughout his hospitalization he was afebrile. The white blood count and sedimentation rate were normal. An electrocardiogram showed changes, but these persisted after the mediastinal emphysema had disappeared so were regarded as secondary to his known rheumatic heart disease. His tuberculin test with 1.0 mg. O.T. was again negative. It had been checked during the episode in January 1945.

In April 1946 he was seen again as a patient in Wisconsin General Hospital. In March 1946 he had an acute febrile illness associated with an acute right lower lobe cavity which was proved tuberculous by gastric aspiration cultures. One week before he was admitted to Wisconsin General Hospital he noted a pain quite similar to that of June 1945. With this attack he was aware of "noise" in the substernal area. The findings were the same as observed before except for changes on the right. His tuberculin test was positive at the time. Subsequent to his tuberculin test in June 1945 he had been at home. His father had an acute illness which was diagnosed as pulmonary tuberculosis. In December 1945 after this exposure a chest roentgenogram had been taken and was reported as normal. By March 1946 the acute tuberculous disease with cavitation was evident. The mediastinal emphysema was present for several days after admission. The disappearance of the associated left pneumothorax was uneventful.

Case 3. A 21 year old man was admitted on September 24, 1945. On September 22, 1945 he had a sudden severe "grip-like" pain just to the left of the sternum at the level of the fourth rib. This had occurred when he was studying. The pain radiated through to his spine and was increased by movement or any jarring motion. When climbing the hill to classes he had observed shortness of breath and on one occasion a tingling and numbness in the little and ring fingers of his left hand. He had also been conscious of a "grating" over the precordium on several occasions. Physical examination confirmed the impression of mediastinal emphysema. Loud precordial knocking sounds were audible at times without the aid of a stethoscope. The area of cardiac dullness was replaced by hyperresonance. A stereoroentgenogram of the chest showed a small translucent band along the left upper cardiac border. There was no evidence of pneumothorax. The physical findings of mediastinal air persisted for six days. He was afebrile and showed no abnormalities in the white blood count or sedimentation rate. An electrocardiogram was within normal limits. His tuberculin test was positive. His hospital stay was eight days.

Case 4. A 22 year old student was seen on June 24, 1946 with a chief complaint of pain "around his heart" which had started five days before but had increased markedly in severity in the preceding 24 hours. He described the pain as sharp and stabbing in nature and non-radiating. Seven years before he had a questionable history of rheumatic fever. The patient was obviously in pain; his skin was cool and moist. Cardiac dullness was replaced by hyperresonance, and the characteristic crunching sounds synchronous with the heart beat were easily demonstrated and were loudest with the patient in a left lateral position. During his hospitalization from June 24, 1946 to June 30, 1946 he was afebrile. A stereoroentgenogram of the chest was normal as were the sedimentation rate and blood count. Electrocardiograms taken in varying positions showed no significant deviations. By June 29, 1946 the signs of mediastinal air had disappeared. There had been a change from the characteristic knocking crunching sounds to those identical with a pericardial friction rub. A tuberculin test done a short time before was negative with 1.0 mg. O.T. and was not repeated.

Case 5. The first woman with mediastinal emphysema was seen on August 23, 1946. This 26 year old student complained of pain in her left chest and midsternal region. Radiation into the neck and left upper arm had been noted. She was aware of a "sensation of rumbling" in her chest. One or two very similar episodes had been experienced previously, but she had not obtained medical attention. The physical signs typical of mediastinal emphysema were demonstrated; i.e., the loss of normal

cardiac area of dullness and the crunching grating sounds synchronous with the cardiac impulse. On roentgenogram a small left pneumothorax was demonstrated. The electrocardiogram and blood count were normal. A tuberculin test with 1.0 mg. O.T. was negative. During her infirmary stay of three days she was afebrile and after a few hours became symptom free.

Case 6. A 26 year old veteran was seen on January 2, 1947. A sudden precordial pain radiating to his left shoulder had its onset while he was in class. Only a mild dyspnea was admitted. He volunteered that he had experienced several previous episodes of similar nature and although some were more painful than this one he had never been seen by a physician. Subsequent to his infirmary admission he was aware of a peculiar crunching sound in his chest. The physical signs were those of mediastinal air and a small left pneumothorax. However, the typical crunching sounds were more difficult to demonstrate than in several of the previous cases and were heard only on deep inspiration. He had no fever, leukocytosis or increased sedimentation rate. A tuberculin test with 1.0 mg. O.T. was negative. An electrocardiogram was not remarkable. On fluoroscopic examination a small left pneumothorax was seen but no clear cut evidence of mediastinal air. After about 24 hours of infirmary stay his symptoms disappeared and he was discharged on January 6, 1947 to be followed in the clinic. When seen on January 8, 1947 he had remained symptom free but a rubbing sound similar to a pericardial friction rub could be demonstrated at the height of inspiration. On January 13, 1947 the signs of mediastinal air had disappeared. Only a very small left apical pneumothorax remained by fluoroscopic examination.

Case 7. On January 6, 1947 a 21 year old student was admitted with a chief complaint of a sharp pain in his left chest and shoulder. This had its onset suddenly a few hours before and was not preceded by unusual activity. Any motion or respiratory effort increased the pain. When he was first examined the characteristic sounds could not be demonstrated but after several examinations a clicking sound synchronous with the heart beat was heard over the second and third interspaces at the left sternal border. No physical signs of the small left pneumothorax demonstrated by roentgenogram were noted. During his five day hospital stay he remained afebrile and had no leukocytosis. An electrocardiogram was normal. A 1.0 mg. O.T. skin test showed no reaction. After two days he became almost symptom free and was discharged on January 11, 1947. When seen in the clinic on January 13, 1947 he had only occasional discomfort on change of position. The signs of pneumomediastinum could still be demonstrated. A very small left pneumothorax persisted over the apical summit. He failed to keep subsequent appointments but when seen recently he stated he had no further difficulty.

Case 8. The second woman in the group was admitted to the infirmary on the same day as the previous case. On January 4, 1947 while in bed she had sudden pain in the right lower sternal area and was aware of her heart pounding. The pain increased in severity and became quite intense if she lay on her back or took a deep breath. The physical examination was difficult to evaluate because of a severe chest deformity secondary to a dorsal kyphoscoliosis. An extremely coarse friction rub was audible and palpable along the right upper sternal border. After careful examination rubbing sounds synchronous with the heart beat were heard over the pulmonic area. As would be expected the chest roentgenograms in postero-anterior and right lateral position were very difficult to interpret. We could demonstrate no pneumothorax or mediastinal air. What could be visualized of the pulmonary parenchyma appeared normal. Because of the chest deformity and cardiac displacement we did not request an electrocardiogram. She had no fever or leukocytosis. Her pain decreased rapidly and she was discharged symptom free on January 8, 1947. When seen in the clinic on January 10, 1947 she stated she had no recurrence of pain

and no abnormal sounds were heard on examination. A tuberculin test on her routine admission study was positive and was not repeated.

Case 9. On January 23, 1947 a 22 year old student was seen in the clinic. During the war he had been pilot of a navy dive bomber and in August 1945 while aboard ship returning home he had a right spontaneous pneumothorax and had been hospitalized for three months and "nothing else found." Since that time he had frequent right chest pain. During the Christmas holidays in 1946 he again had right sided chest pain and was very short of breath. He consulted his local physician who told him he "had all the symptoms of tuberculosis." The patient was reluctant to accept this diagnosis because he knew his tuberculin test was negative when he entered school in March 1946 and he had a normal chest roentgenogram in October 1946. He recovered sufficiently to return to school and continued to improve until three or four days before he reported for examination. At that time he had more pain in the right chest. Examination showed a right pneumothorax which was confirmed by fluoroscopic examination. No mediastinal emphysema could be demonstrated by physical signs. He refused infirmary care but returned for observation on January 25, 1947. On this date he agreed to enter the hospital because of the finding of increased pneumothorax. Typical crunching sounds were demonstrated at the base of the heart on held inspiration. On January 26, 1947, 600 c.c. of air were removed from the right pleural space, an initial pressure reading of -6 and -8 cm. of water was obtained. No final pressure determination could be obtained, apparently due to expansion of the lung over the tip of the aspirating needle. The patient remained afebrile. The white blood count and electrocardiogram were normal. His tuberculin test with 1.0 mg. O.T. remained negative. Expansion of the lung was progressive without further aspirations. On January 29, 1947 he was discharged essentially asymptomatic. When seen in the clinic on January 31, 1947 a small right pneumothorax persisted and rubbing sounds identical with those of a pericardial rub were heard. Due to a misunderstanding in instructions he did not return until February 10, 1947. He again had chest pain but this was pleural in character and was over the lower lateral chest wall. No signs of pleural friction rub could be demonstrated, nor could any signs of mediastinal air be found. On fluoroscopic examination the right pneumothorax had disappeared and only a slight pleural reaction at the right sulcus remained. A few days later he reported that the chest pain had completely disappeared.

Case 10. A 34 year old graduate student was admitted on February 15, 1947. On February 14, 1947 while eating breakfast he noted the onset of pain over the left chest anteriorly and over the precordium. His pain was increased on motion and deep breathing. On moderate exercise a mild dyspnea had been present. The physical findings were those of a left pneumothorax and mediastinal emphysema. As noted in the previous cases the precordial area was hyperresonant and the usual knocking crunching sounds were heard over the entire precordium. Fluoroscopic examination on February 15, 1947 revealed almost complete collapse of the left lower lobe, but the lobe was aerated. The upper lobe was not collapsed. There was a large pocket of air between the upper lobe and the heart shadow. Whether this was in the mediastinal tissues or a pneumothorax pocketing could not be determined. By the morning of February 16, 1947 the pneumothorax had increased so that both lobes were collapsed to small airless "nubbins." In spite of this increased pneumothorax the patient was much more comfortable. Mediastinal air was present to physical examination.

On February 17, 1947, 1000 c.c. of air were removed from the left pleural space. The initial pressure was atmospheric and the final reading was -1 to -3. On fluoroscopic examination the next morning there had been no appreciable decrease in pneumothorax so 1,400 c.c. of air were removed with final pressure readings of -16 to -20. An immediate fluoroscopy showed some mediastinal shift to the left. The left upper lobe had not become air containing although only about 15 per cent

pneumothorax persisted. On February 19, 1947 aeration of both lobes was complete and there remained only about 10 per cent residual pneumothorax. An electrocardiogram was normal. Tuberculin tests with .01 and 1.0 mg. O.T. were negative. There was no significant leukocytosis.

On February 22, 1947 he was seen as an outpatient and reported that he still had some pain but felt quite well. Signs of pneumomediastinum persisted and there was evidence of this air on a single chest roentgen-ray in a small translucent zone along the left cardiac border. There remained a small left pneumothorax.

On February 25, 1947 the signs of mediastinal air had disappeared. By February 28, 1947 there was no evidence of mediastinal or pleural air on fluoroscopy. He felt entirely well and had returned to classes although he was still cautious about overexertion.

It is interesting to note that a roentgenogram taken March 17, 1943 showed evidence of small emphysematous blebs at both apices. There had been no significant change on the right side, and on the left side comparison of densities was difficult due to pneumothorax.

Case 11. On February 24, 1947 a 26 year old student was examined in the clinic. On February 5, 1947 while in bed he experienced a sudden pain in the lower anterior left chest. At this time he stated he had just recovered from a rather severe "cold" which had been accompanied by a cough. The pain was increased by deep breathing and was accompanied at times by a sound "like tissue paper crackling" over the lower sternal area. He was seen by a local physician who taped his left chest for "pleurisy." However, the patient experienced no relief from this and because of continued pain he reported to the student clinic and a chest roentgenogram was secured on February 19, 1947. This showed a small left pneumothorax. Because of our interest he was checked for mediastinal emphysema on February 24, 1947. At this time no physical sign of the left pneumothorax could be demonstrated. There was loss of cardiac dullness. His precordium was hyperresonant. A typical crunching sound of pneumomediastinum was present. Because of his relative freedom from symptoms and the long continued course with some improvement he was very reluctant to enter the hospital so he was seen again on February 26, 1947 in the clinic. At this time he was feeling better. The signs of mediastinal air persisted. When seen on February 28, 1947 the pain had increased and there was evidence of mediastinal air on fluoroscopic examination with the patient in the left anterior oblique position. At this time he was convinced that hospital care was desirable. On March 1, 1947 at 8 p.m. he had a sudden sharp pain in the epigastrium and in the right lower quadrant. He also noted some pain referred to the left trapezius at this time. Examination showed generalized abdominal tenderness with some rebound tenderness. He had no febrile response to this. By the next morning he was free of pain and had no significant physical finding. Fluoroscopic examination revealed no air under the diaphragm and no recurrence of the left pneumothorax.

On March 3, 1947 he developed a very harassing cough accompanied by a low grade fever. This was entirely similar to the tracheobronchitis which was prevalent in the student body. He had been in the same room with Case 12 until that patient had been recognized as having tracheobronchitis. With the use of steam inhalations and codein his cough was fairly well controlled and gradually disappeared. He continued to have physical signs of mediastinal emphysema until March 6, 1947. All his symptoms disappeared and he was discharged on March 11, 1947. His sedimentation rate and leukocyte count were normal. A tuberculin test with 1.0 mg. O.T. was negative. An electrocardiogram showed no significant deviations.

Case 12. A 24 year old man was admitted to the infirmary on February 28, 1947. His chief complaint was substernal pain. He stated that he had noted several transitory attacks of substernal pain during the past month. A more severe episode oc-

curred at 4:30 p.m. on February 27, 1947 and lasted about five minutes. The pain radiated directly through to his back. The morning of February 28, 1947 a hacking cough developed. He had no shortness of breath. On physical examination there was no evidence of pneumothorax. There was hyperresonance over the precordium. Typical knocking rustling sounds synchronous with the heart beat were heard over the lower sternal area and were loudest with complete expiration. During the evening of February 28, 1947 his temperature rose to 104° F. and his cough became very annoying. On March 1, 1947 the signs were essentially unchanged. His fever subsided promptly as did the cough. On March 4, 1947 his symptoms and signs had disappeared completely and he was discharged. An electrocardiogram was normal except for tendency to right axis deviation. His total leukocyte count was 8450 and 81 per cent polymorphonuclears were present. A tuberculin test done previously was positive and was not repeated. His chest roentgenogram showed no evidence of pneumothorax or mediastinal air and was unchanged from previous roentgen-rays in 1942.

Case 13. A 29 year old woman was admitted to the hospital on March 3, 1947. Her complaint was a "tight feeling in the chest." For three weeks she had noted episodes of substernal discomfort "like a hand gripping her." On the afternoon of admission while in class she had a more severe attack. She complained of feeling faint when first seen. She had observed that the pain was increased markedly by change in position. On physical examination her skin was cold and clammy and the fingernails were subcyanotic. Pulse rate was 80 per minute, blood pressure 132/82. The area of cardiac dullness was replaced by a hyperresonance. The characteristic crunching sounds were not demonstrated until the following day when they were heard clearly at the left third interspace at the sternal border. These sounds persisted but diminished greatly until March 6, 1947 when they were no longer audible, and she was discharged. On March 8, 1947 when she returned to the clinic she still had very slight precordial pain. There were no signs of mediastinal emphysema or pneumothorax by physical examination or fluoroscopic examination. Her tuberculin test remained negative. The blood count was normal. No electrocardiogram was taken. A chest roentgenogram during her infirmary stay showed no abnormalities.

Case 14. A 19 year old student was admitted on March 10, 1947 with a chief complaint of chest pain. Two days before she noted an abrupt onset of mild pain in the left anterior chest which became worse progressively. Her pain was accentuated by coughing, any motion and especially by movement of her left arm. She complained of severe pain over the fourth costochondral area when she moved her left arm or on pressure over this area. When first seen in the clinic the characteristic sounds of mediastinal emphysema were not heard. Because of a history of having been in a "scuffle" shortly before the onset of the pain the diagnosis of a rib fracture was considered, but there was no evidence of any fracture by roentgenogram. After being admitted to the infirmary the usual signs of mediastinal emphysema were elicited. The precordium was hyperresonant and loud crunching sounds were audible over the heart and synchronous with the heart beat. The hyperesthesia in the fourth costochondral area persisted about two days. On admission she had a fever as high as 101° F. and the following day the maximum fever was 101.8° F. She complained of some generalized malaise and mild sore throat. Her leukocyte count was normal. A tuberculin test had been positive previously and was not repeated. On chest roentgenogram there was no evidence of pneumomediastinum or pneumothorax. An electrocardiogram was normal. After March 11, 1947 she remained afebrile and her symptoms rapidly disappeared. On March 14, 1947 only an occasional rubbing sound was heard over the pulmonic area. As she was asymptomatic she was discharged to continue observation in the clinic. When seen on March 22, 1947 she was entirely symptom free and no evidence of pneumomediastinum could be demonstrated.

Discussion

During the past four years we have seen a total of 20 students with spontaneous pneumothorax, mediastinal emphysema or a combination of these two conditions.* In this same interval we have seen several other individuals in whom the diagnosis was considered because of the history and course, but in whom diagnostic physical signs could not be demonstrated nor could air in the mediastinal structure or along the pulmonary vessels be demonstrated by roentgenogram. However, in several of these individuals there was hyperresonance over the precordium and a peculiar crepitus synchronous with respiration but not with the heart beat.

The history of mediastinal emphysema is quite characteristic. The pain is rather sudden in onset and may vary a great deal in severity. The most common location of the pain is substernal with frequent radiation straight through to the back or into the left neck or shoulder. Occasionally the pain may radiate in the manner of angina pectoris into the little and ring fingers of the left hand. The association of pain with change in position or with any jarring motion is noteworthy. Six of the 14 patients with mediastinal emphysema were aware of peculiar sounds over the precordium.

The physical signs are distinctive. The most characteristic is the crunching sound synchronous with the heart beat. This may vary greatly during the episode and with change in position or phase of respiration. The intensity of the sounds bears no relationship to the severity of the patient's symptoms; often the patient is almost free of pain when the crunching is most pronounced. Frequently the sound may be identical to that heard in pericardial friction rub. This type was heard almost routinely after the loud crunching sounds had disappeared. In Case 8 a loud pleural friction rub was heard along the right sternal border in addition to the rubbing sounds synchronous with the heart beat. In our series hyperresonance over the precordium was a constant finding. None of the group showed any physical evidence of subcutaneous air. In only one individual was retroperitoneal air dissection suspected.

We were able to demonstrate mediastinal air by roentgenogram or fluoroscopic examination in only three of the 14, although repeated examinations were done in various positions. Likewise we found no subcutaneous air in the neck or elsewhere. Air in the mediastinum is difficult to visualize unless it is localized or relatively large in amount. This circumstance would be anticipated due to lack of contrast because of the air containing structures surrounding the mediastinum. The presence of an associated pneumothorax increases this difficulty.

Although electrocardiograms were obtained in the majority of the group and taken in varying positions we were unable to demonstrate any character-

* Since this paper was submitted the author has seen seven students with spontaneous pneumothorax. These pneumothoraces all occurred on the right. In six of the seven there was an associated mediastinal emphysema.

istic pattern for mediastinal emphysema with or without pneumothorax. The value of the electrocardiogram, as has been pointed out previously, lies in the exclusion of the more serious conditions which might be confused with this symptom complex; i.e., coronary occlusion and pericarditis.

In this series the pain and symptoms were not of the severity to be confused readily with coronary occlusion or pericarditis. In both the groups with spontaneous pneumothorax and mediastinal emphysema the diagnosis might have been overlooked or attributed to muscle strain, neuritis, cardiospasm, pleuritis or so-called "witch's stab."

Likewise we found these individuals to have no significant change in the leukocyte count or sedimentation rate. The three patients who demonstrated a febrile response (Cases 11, 12 and 14) were diagnosed as having an unrelated tracheobronchitis. In these patients the symptoms of mediastinal emphysema preceded the onset of the acute tracheobronchitis. All were seen at the time when the incidence of this infection, probably virus in type, was prevalent in the entire student body. Although we used no chemotherapy or antibiotics, no complications developed as the result of this superimposed disease. Their courses were entirely comparable to those patients having similar infection without mediastinal emphysema. In spite of the difficulty in controlling the cough accompanying the tracheobronchitis, none of these individuals had evidence of any marked increase of mediastinal emphysema by signs or symptoms. The duration of symptoms varied widely. Several of the cases from the history had continued air leaks or repeated episodes of alveolar rupture. The evidence of mediastinal emphysema to physical examination may be extremely transient as noted in Case 1.

Recurrences of mediastinal emphysema have been pointed out by Schwartz, McIlroy and Warren,[9] and by Schendstok.[11] In Case 2 there was a verified recurrence of mediastinal emphysema and left pneumothorax as well as one previous episode of right pneumothorax. In Cases 1 and 9 there had been previous episodes of pneumothorax verified by roentgen study. In Cases 5 and 6 the history was very suggestive of previous pneumothorax and/or mediastinal emphysema. Of the group with pneumothorax without recognized mediastinal emphysema one of the six had a history of very probable pneumothorax and two had observed recurrences, one within two weeks after expansion and the other the following year. The majority of the entire group is too recent to evaluate from the standpoint of recurrences.

As observed in previous reports there is a high incidence of associated pneumothorax. Of the 14 with mediastinal emphysema seven had pneumothorax, six on the left and one on the right. The reason for the predominance of left pneumothorax is unexplained although to our knowledge only one case of right pneumothorax associated with pneumomediastinum has been recorded.[9] The amount of pneumothorax is not constant but is not necessarily small as evidenced by Cases 9 and 10. In our experience the occurrence of pneumothorax does not alter the course of a mediastinal emphysema. The appearance of recognized mediastinal emphysema in Case 9 was in the

face of an increasing pneumothorax. In Case 11 the mediastinal emphysema increased after the pneumothorax had disappeared and although a very probable episode of retroperitoneal air dissection occurred there was no recurrence of the left pneumothorax.

Tuberculin testing was done on the entire group except those who were known to be tuberculin positive from their student health records. Of the 20 students only four were tuberculin positive and these were all tuberculin positive at the time of their routine admission tuberculin tests. This percentage is essentially the same as in the entire student body. None of the individuals showed any lesions regarded as tuberculous in nature. The presence of pleural adhesions with pneumothorax was not regarded as tuberculous in origin and was seen only in two individuals who were tuberculin negative. Of the entire group only one student, Case 10, had roentgen evidence of emphysematous blebs. The student with the severe chest deformity may well have areas of unrecognized pulmonary emphysema due to overdistention of portions of the lung.

Of the entire series males have outnumbered females 14 to 6. This is not a disproportionate number of males considering the sex ratio in the University population.

Treatment of spontaneous pneumothorax in this series has been symptomatic. It has been our policy to hospitalize the individuals if they are seen shortly after the onset or if they are having acute pain or other symptoms. With the spontaneous pneumothoraces which are small and relatively symptom free when they first present themselves for examination several days after the onset, we have observed them frequently as outpatients to check the progress of expansion. This policy has been adopted from previous experience in the Student Health Service and from other patients who are not included in this study. Normal respiratory effort does not increase the intrabronchial pressure and therefore should not serve to continue the leak through the alveolar rupture. The patients are cautioned against the possible ill effect of any effort with a closed glottis, such as lifting, coughing, etc. Aspirations of pleural air were done to relieve dyspnea, or if the pneumothorax was large and asymptomatic, to hasten reëxpansion. If the pulmonary parenchyma is normal, the bronchial tree patent and pleura normal, it is impossible to create any significantly negative intrapleural pressure with ordinary aspirations.[23] Therefore, we see no reason to fear that aspiration is going to reopen any rupture of alveolar wall. If, as occasionally occurs, the lung or portions of the lung are atelectatic, as in Case 10, we believe that aspiration is indicated to allow prompt reaeration of the lung before infection or other complications of bronchial occlusion occur. If a persistent leak is present it may be recognized by failure of change of manometric readings or failure of expansion following aspiration of air. The treatment of the rare case in whom there is persistent or frequently recurrent pneumothorax is not within the scope of this report.

The benign course of the average spontaneous pneumothorax and our earlier experience with mediastinal emphysema have encouraged us to treat these individuals in a similar manner. If their symptoms are acute and the onset recent with increasing symptoms, we hospitalize them promptly for symptomatic treatment and relief of pain. At the same time close medical attention is available if the rare complication of serious interference with venous return or bilateral pneumothorax should occur. As soon as the patient is symptom free and the signs of mediastinal air are decreasing he is discharged to be followed as an outpatient. As the majority of cases show no correlation between the onset of symptoms and physical exertion, the probability of preventing recurrence by continued bed rest seems unlikely. Recurrences or sudden increase in symptoms have been reported in patients who are at bed rest.[9, 11]

These individuals must be reassured that they have no serious pulmonary or cardiac pathology. The rather dramatic onset with occasional severe pain is alarming to the individual. This psychic trauma plus continued bed rest for periods of weeks will serve to convince a fair number of patients that they have serious pulmonary or cardiac disease and they will become cardiac or pulmonary invalids. The problem of recurrent episodes must be admitted but not stressed.

The use of sulfonamides or antibiotics as a prophylaxis against mediastinitis is not recommended. They should be reserved for concurrent or complicating infections. Cough should be controlled to prevent the marked increase in intrabronchial pressure.

Conclusions

1. Twenty cases of spontaneous pneumothorax and pneumomediastinum were observed in a four year period. There were six cases of pneumothorax without recognized mediastinal air, seven individuals with mediastinal emphysema without recognized pneumothorax and seven patients with a combination of the two conditions.

2. In this series there was no significant variation in the incidence among males and females considering the disproportion among the university population.

3. Short periods of symptomatic treatment with early ambulatory observation have been entirely satisfactory in our experience.

4. There have been no complications in 14 cases of spontaneous mediastinal emphysema.

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HYPERTENSIVE CEREBRAL SWELLING, A CHARACTERISTIC CLINICO-PATHOLOGIC SYNDROME *

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This presentation aims to analyze the brain findings of only such cases of hypertensive brain disease as are characterized by a sudden onset and rapid progression of the following clinical symptoms and signs: Severe headache, drowsiness, confusion, restlessness and delirium accompanied by signs of increased intracranial pressure, such as elevation of spinal fluid pressure and bilateral papilledema; and occasionally by convulsions, impairment of vision and weakness of extremities. This acute clinical syndrome may last for days and then completely remit, or it may in some instances be the cause of rapid death.

Before the pathologic findings characteristic of this condition are presented in detail, it would seem appropriate to review the cerebral lesions pathognomonic for hypertensive brain disease in general.

In previous contributions [1, 2] attention was called to vascular alterations in hypertensive encephalopathy. The histologic changes which were regarded as typical consisted of hyaline degeneration and fibrotic thickening of the vessel wall with narrowing or complete obliteration of the vascular lumina. It has been emphasized that these vascular changes confined to arterioles and capillaries are different from those found in arteriosclerosis and are to be interpreted as a special form of hypertensive arteriolopathy. The alterations of the nervous parenchyma characterized by diffusely scattered small foci of old and recent softening were interpreted as secondary to the vascular lesions.

In addition to the arteriolar changes two types of *venous* alterations were recently described [3, 4]: (*a*) Reversible changes characterized by stasis, congestion and distention of the vascular lumina; (*b*) structural lesions of the vessel wall manifested by advanced signs of degeneration, necrosis and/or an extreme degree of atrophy.

Whereas the arteriolar changes were interpreted as significant for the diffuse focal areas of softening and gliosis of the nervous parenchyma typical of hypertensive encephalopathy, the alterations of the cerebral veins were regarded as responsible for the origin and pathogenesis of massive intracerebral hemorrhages so often encountered during the terminal phase of hypertensive brain disease.

The present investigation is based upon 12 cases that have been subjected to histopathologic study. No attempt will be made to describe the

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findings in each case. Two illustrative cases, however, are presented herewith in detail.

Case Reports

Case 1. A 34 year old colored male was known to have had high blood pressure for a period of more than one year. He was apparently well until four months prior to his admission to the hospital, at which time he began to have brief spells of visual difficulty in which he said he couldn't see. In addition he complained of shortness of breath on exertion and occasional swelling of the feet. For the 10 days preceding admission the patient had complained of severe occipital and frontal headaches. An hour and a half before his admission he became confused, delirious and, according to the information given by his wife, "had talked out of his head."

On admission the patient was semi-stuporous; he responded only occasionally to simple commands.

There was a fine horizontal nystagmus; the eyes were deviated toward the right. The optic discs were clearly outlined; there were extreme narrowing of the arteries and pronounced fullness of the veins. Fresh hemorrhages were seen in the right retina.

Resistance of the limbs to passive movement was reduced. On the evening of admission the patient was thought to have a left hemiparesis; on painful stimuli he moved the right lower extremity slightly better than the left. The abdominal reflexes were absent. There was a right Hoffman response. Pyramidal signs were equivocal on both sides.

The heart was enlarged to the left and the apex beat was forceful. There was a harsh systolic murmur to the left of the sternum at the second interspace and in the pulmonic area. There was mild edema of the ankles. Respiration was fast and noisy.

Clinical Course: The patient remained stuporous; the edema increased and spread to involve the trunk and face. The patient died 66 hours after his admission to the hospital.

Laboratory Data: The systolic blood pressure ranged between 240 and 280 mm. of mercury (on occasion, beyond the range of the manometer), the diastolic between 120 and 150. The blood analysis was as follows: hemoglobin 11 grams, red blood count 3.8 million per cubic millimeter, white blood count 19,500 per cubic millimeter, the blood urea nitrogen 100 mg. per 100 c.c., blood Kahn negative. One urinalysis showed a specific gravity of 1.010 and a three plus albumin test. There were 70 to 80 white blood cells and 4 to 5 red blood cells per high power field with a few epithelial cells in the smear.

A lumbar puncture revealed an initial pressure of 385 mm. of water. After the removal of 6 c.c. of fluid resembling water, the final pressure was 190 mm. There were four white blood cells and 12 red blood cells per cu. mm. The protein was 130 mg. per 100 c.c., and the Wassermann reaction was negative. There was a first zone gold curve (4442210000).

Pathologic Findings: The extraneural findings were chronic pyelonephritis, nephrosclerosis, hypertrophy and dilatation of the heart, and generalized arteriosclerosis.

On gross examination of the brain the gyri were flattened and broadened, the sulci narrowed. There was an old area of softening about the posterior portion of the left Sylvian fissure. There was a well-defined cerebellar pressure cone. Although the temporal lobes appeared generally swollen, there was no uncal herniation. There was sclerosis of the vessels of the circle of Willis.

Coronal sections through both hemispheres revealed broadening of the white matter, compression and narrowing of the cortical gray matter and almost complete obliteration of the lateral ventricles (figure 1). There was a small area of recent

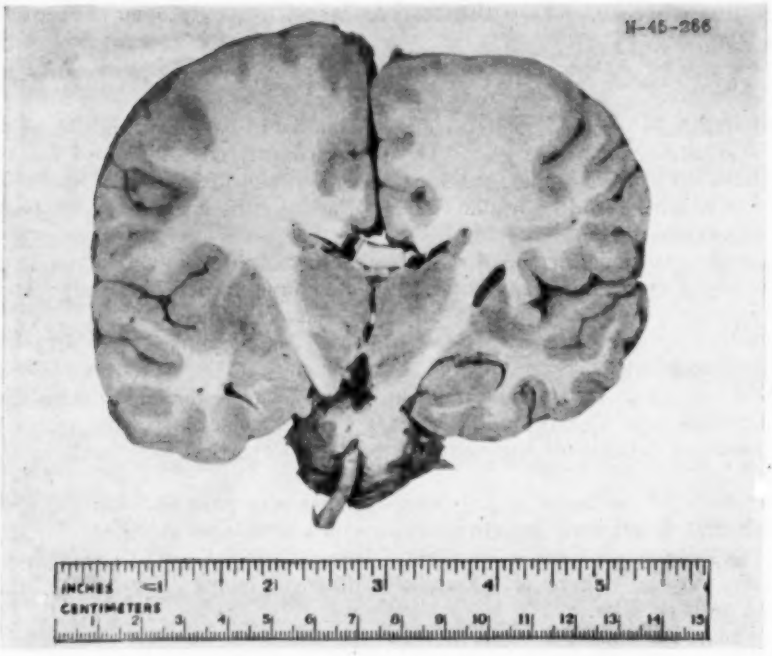

FIG. 1. *Case 1.* Diffuse swelling of the white matter of both hemispheres. Note the compression and narrowing of the cortical gray matter and the obliteration of the lateral ventricles. (The corpus callosum was severed at autopsy to allow for better penetration of the formalin solution.)

FIG. 2. *Case 1.* Irregular swelling and partial destruction of the nerve fibers of the white matter. Bodian silver impregnation; × 220.

softening transecting the left internal capsule near the head of the caudate nucleus. In the white matter of the left occipital lobe there was a ball hemorrhage measuring 8 mm. in diameter. The scar of an old softening in the right hippocampus was observed; and also an old cyst 1 cm. in length involving the lateral portion of the left internal capsule and the mesial portion of the globus pallidus.

The microscopic examination disclosed tremendous swelling of all the constituents of the nervous parenchyma. These changes hardly would have been seen in preparations stained with hematoxylin and eosin; stained by the Bodian and Loyez methods the characteristic findings of brain swelling were obvious (figure 2). The majority of the nerve fibers and myelin sheaths were irregularly swollen; numerous fusiform varicosities were found throughout their course. The glia did not escape the process of swelling. In all sections taken from the white matter there was rarefaction of the tissue. The subcortical U-fibers were relatively well preserved. The cortical ribbon was compressed, but otherwise was normal.

There were two principal types of vascular abnormalities: arteriolar hyalinization characteristic of hypertensive arteriolopathy, and congestion and stasis of veins associated with degeneration and atrophy of their walls.

Case 2. A 38 year old colored male was perfectly well until four weeks before admission to the hospital, when his vision began to fail. Recently he had noticed bloody urine. No cardiac symptoms were present.

On examination papilledema associated with hypertensive neuro-retinopathy was found. The heart was enlarged to the right. The blood pressure was 244/156.

The Wassermann reaction in blood was negative; blood urea nitrogen at the time of the admission was 26 mg. per 100 c.c.; a few days before death blood urea nitrogen was 60 mg. per 100 c.c.

He grew steadily worse; four weeks after his admission he became lethargic and developed right hemiparesis. Coma deepened and death occurred the following day.

The gross pathologic abnormalities at autopsy were pulmonary congestion and edema, malignant nephrosclerosis, marked hypertrophy and dilatation of the left ventricle of the heart.

Gross Description of the Brain: The brain appeared markedly swollen, the gyri were extremely flattened, the sulci narrowed or completely obliterated. The leptomeninges overlying the surface of the brain were slightly thickened. On the under surface of the brain there was to be seen an uncal herniation measuring 3 mm. in width. There was an obvious cerebellar pressure cone, particularly marked on the left. The lumina of the larger blood vessels at the base were dilated; the vessel walls were thickened and harbored a few sclerotic plaques. Coronal sections disclosed a far advanced degree of swelling of both cerebral hemispheres (figure 3). In addition, there was found in the left putamen a hemorrhagic area measuring 1.5 cm. in diameter. An old area of softening, bounded by a yellowish brown discoloration, was present in the left thalamus.

Microscopic Findings: Sections were taken from the cortex of the parietal, frontal and occipital lobes, basal ganglia, hypothalamus, cerebellum and pons, and were stained with hematoxylin and eosin, hematoxylin and van Gieson, and cresyl violet; the Loyez and Bodian methods were also employed.

The histologic examination revealed two principal types of abnormalities: (1) changes of the brain parenchyma and (2) vascular alterations.

The main histologic alterations, involving large areas of the white matter of both hemispheres, consisted of acute swelling of all constituents of the nervous parenchyma. A striking manifestation of the process was best seen in sections stained by the Bodian silver impregnation method (figure 4). Most nerve fibers were considerably swollen, intensely stained and irregularly outlined. Some of the axons disclosed advanced degenerative lesions characterized by fragmentation; occasionally they were broken

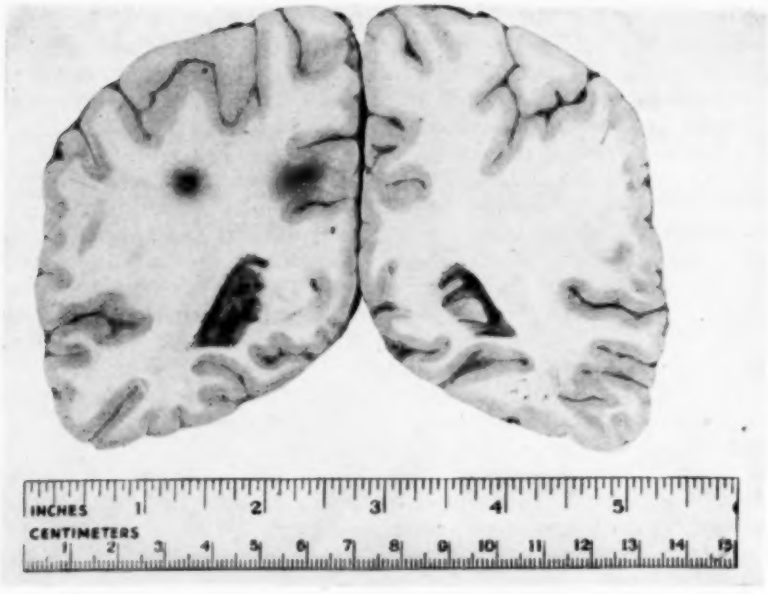

FIG. 3. *Case 2.* Diffuse swelling of the white matter of both hemispheres. Note the "ball hemorrhage" on the right.

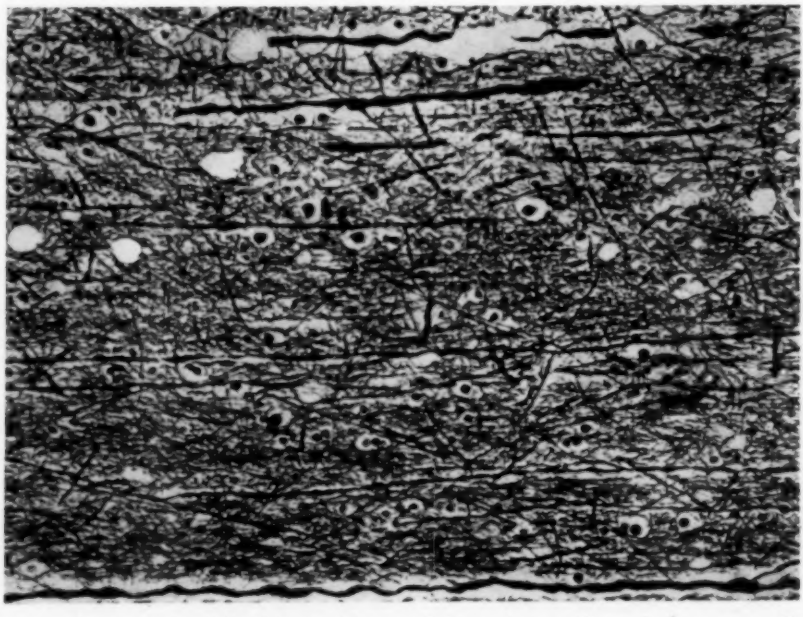

FIG. 4. *Case 2.* Considerable swelling and irregular outline of the nerve fibers of the white matter. Note the swollen oligodendroglia cells. Bodian silver impregnation; × 220.

into granular debris or were undergoing fragmentation. In addition there was to be seen a diffuse swelling of the oligodendroglia cells. Loyez preparations revealed diffuse and extensive swelling and irregular beading of the myelin sheaths. These changes were most prominent in the white substance. Many of the myelin sheaths were broken up into globules.

There was tremendous distention of the perivascular spaces (figure 5) which harbored large masses of serous fluid and a few cellular elements, chiefly histiocytes and macrophages.

In all sections structural changes in the blood vessel walls were frequently observed. These consisted of marked thickening, homogenization and hyalinization of the capillaries and arterioles (figure 6). In sections stained with hematoxylin and van Gieson, and by the Bodian silver method, it could be seen that the essential pathologic process was characterized by hyaline degeneration and thickening of the vessel wall. The vessel lumina appeared extremely narrow or completely obliterated. In some of the capillaries and arterioles the entire vessel wall appeared to be transformed into a strand of connective tissue. The mesenchymal fibrils running longitudinally or transversely were devoid of elastin and easily impregnated with the Bodian silver stain, and stained red with the hematoxylin and van Gieson stain. Some of the smaller blood vessels were surrounded by small accumulations of lymphocytes and a few fat granule cells (figure 6). These cells usually were confined to the perivascular space and did not infiltrate the vessel wall.

Summary of Pathologic Findings: The outstanding pathologic brain changes found in all cases consisted in a tremendous degree of cerebral swelling. The gross findings were characterized by a considerable increase in volume of both hemispheres, flattening of the gyri and narrowing or obliteration of the sulci; considerable enlargement of the central and subcortical white matter with consequent narrowing and compression of the cortical gray; loss of demarcation between white and gray matter; decrease in size or complete obliteration of both lateral ventricles.

In addition there were disseminated ball hemorrhages in various regions of the brain tissue. Only occasionally (in two cases out of 12) were there massive hemorrhages.

The microscopic findings were identical with those recently described as characteristic for the early reversible stage of cerebral swelling, designated as cerebral tumefaction.[5] As already emphasized, microscopic findings characteristic of cerebral tumefaction may easily be overlooked in routine sections stained with hematoxylin and eosin. They are best noted with careful study of silver impregnations, such as Bodian or Bielschowsky methods.

The pertinent histologic findings may be summarized thus: (1) parenchymatous changes with evidence of swelling of the nerve fibers, myelin sheaths, glia and particularly of the oligodendroglia; (2) vascular alterations confined to the small veins and capillaries characterized by (*a*) congestion and stasis, and by (*b*) swelling and degeneration of the endothelial cells. These changes were predominant in the white matter.

In addition there were arteriolar changes characteristic of hypertensive arteriolopathy.[4] Only occasionally were there seen small focal areas of softening or glial scarring.

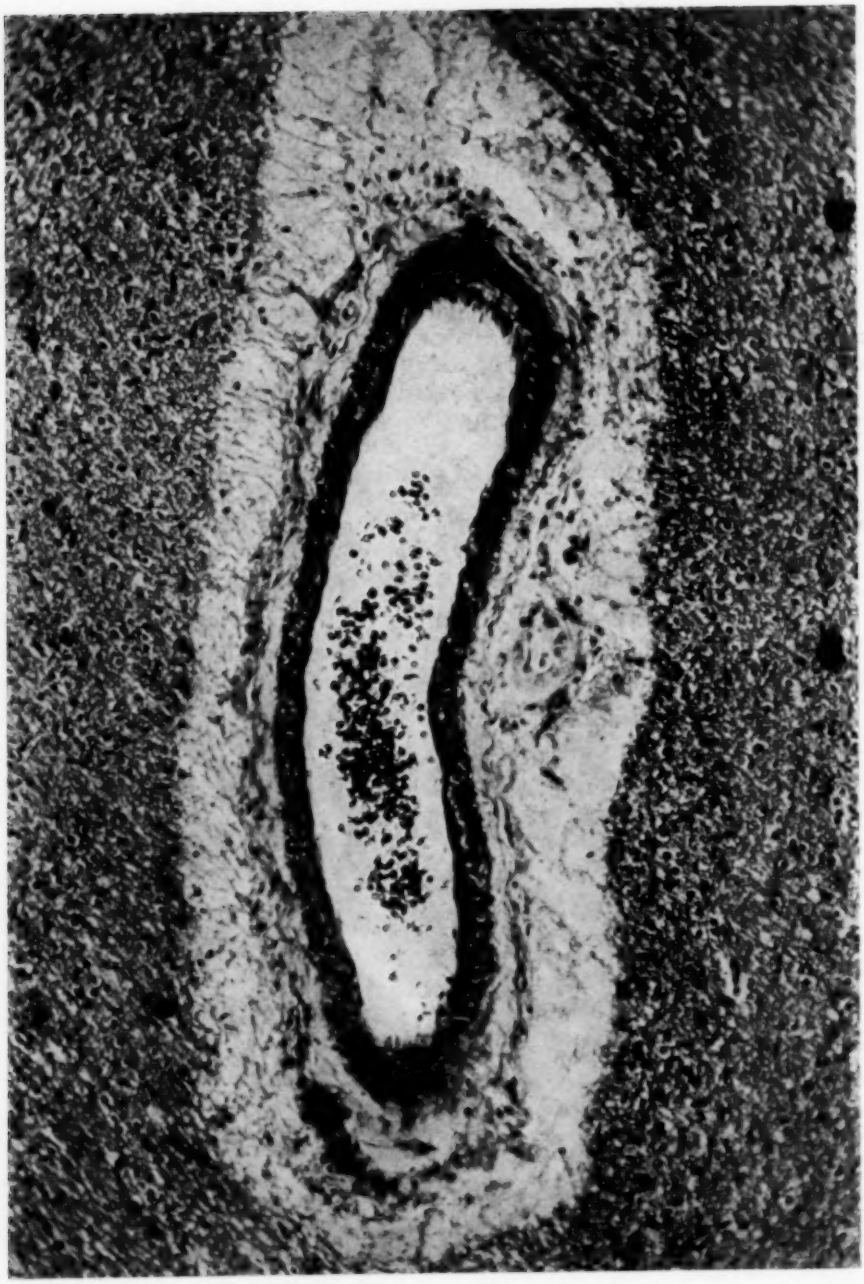

FIG. 5. *Case 2.* Distended perivascular spaces harboring large masses of serous fluid and a small number of macrophages. Hematoxylin eosin; × 180.

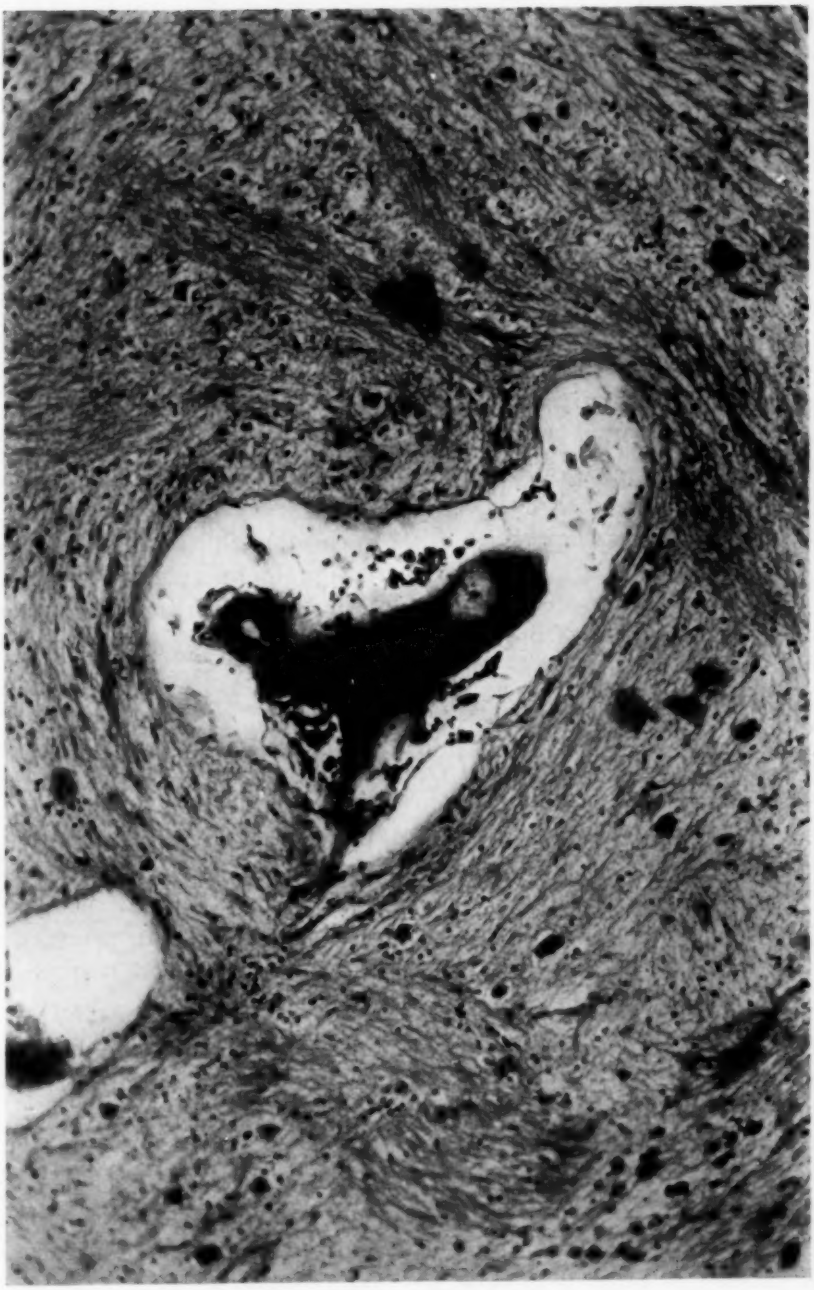

FIG. 6. *Case 2.* Far advanced form of hypertensive arteriolopathy. Hematoxylin and eosin; ×180.

Clinicopathologic Correlations

The diffuse swelling of wide areas of cerebral tissue explains why the clinical symptomatology occasionally resembles the acute manifestations of brain tumor. The remarkable parallelism may be attributable to the fact that the clinical syndrome under discussion rests upon the effect of an acute increase in the bulk of the brain with consequent increase in intracranial pressure. The clinical manifestations of papilledema and considerable elevation of the cerebrospinal fluid pressure, noted in almost all cases under observation, corroborate this conclusion.

As already emphasized, the fulminating course and alarming clinical symptoms may occasionally end in rapid recovery with complete disappearance of most of the clinical symptoms. Needless to say, the reversibility of the process is best explained by the relatively mild degree of the pathologic findings characteristic of the early stage of cerebral swelling. Reversible vascular alterations, associated with increased permeability of the vessel wall for serous fluid, have been stressed by the author as the most significant feature in the pathogenesis of cerebral swelling.[5] The functional vascular alterations are characterized by a complete relaxation of the vessel walls of the smaller veins and capillaries, resulting in enormous distention and stasis. These vascular changes are associated with signs of increased permeability for serous fluid of the vessel walls, thus leading to an increase in intra- and extracellular fluid content of the nervous parenchyma.

The clinical syndrome under discussion previously has been referred to as "vascular crisis" (Pal[6] and Allbutt[7]), "pseudo-uremia" (Volhard[8]), "hypertensive encephalopathy,"[9] and, more recently, as "malignant hypertension."[10] Pal and Allbutt offered vascular spasm as an explanation for the pathogenesis of the syndrome. The histologic examination of the brain in our series of cases failed to reveal morphologic evidence of angiospastic phenomena. Venous and capillary distention were the predominant vascular alterations. However, it is possible that the final relaxation of the smaller blood vessels with resultant venous distention may have been preceded by brief angiospastic phenomena which, owing to their transient nature, cannot be detected morphologically.

Clinical Considerations

Clinical manifestations referable to nervous system alterations in cases of hypertensive cerebral swelling may be summarized briefly, as follows: Sudden onset of an increasingly severe headache, with rapid development of progressive drowsiness; confusion and delirium, frequently associated with vomiting of projectile character; impairment of vision and generalized convulsions. Bilateral papilledema and marked elevation of the cerebrospinal fluid pressure, which are the most consistently observed findings, are pathognomonic enough to permit clinical recognition of the syndrome. The notable

parallelism between this syndrome and the manifestations of a rapidly expanding space-consuming intracerebral process (malignant neoplasm, cerebral abscess) explains the ease with which the two conditions may be confused. The presence of arterial hypertension, however, in combination with hypertensive retinopathy and with signs and symptoms of hypertensive cardiovascular disease, permits differentiation of hypertensive cerebral swelling from cerebral space-consuming lesions.

In the survey of clinical data of the 12 cases of the present study, particular attention was given to clinical manifestations antecedent to the fatal development of hypertensive cerebral swelling, such as cardiovascular and renal disorders, clinical evidence of uremia, earlier episodes of focal or cerebral involvement and, finally, the character of the cerebrospinal fluid both preceding and during the fatal illness.

Age: The majority of cases of hypertensive cerebral swelling occurred between the ages of 24 and 63. The average age was 46.

Duration of Hypertension: It was not always possible to establish accurately the duration of hypertension. Exploration of various sources for earlier blood pressure measurements yielded the following data: The mean duration of arterial hypertension preceding the fatal illness was 4.1 years. In all cases but one both the systolic and diastolic pressures were extremely high. The systolic ranged between 200 and 270; the diastolic between 150 and 165.

Optic Fundi and Retinal Arterioles: Examination of the optic fundi is of paramount significance for the recognition of hypertensive cerebral swelling. In all but three cases (in one case the examination of the fundi was not made), there were definite signs of papilledema ranging from "blurring" of the disc margins to pronounced swelling of from 3 to 4 diopters.

Examination of the retina disclosed in all cases various stages of hypertensive retinopathy characterized by constriction and thickening of the retinal arterioles, cotton-wool exudate, recent and old hemorrhages and venous congestion.

Spinal Fluid Changes: Strikingly characteristic for hypertensive cerebral swelling is the considerable elevation of the spinal fluid pressure.

In 10 out of the 12 cases, the spinal fluid pressure was high above the norm, ranging between 350 and 470 mm. of water. The other two cases disclosed spinal fluid pressures of 230 and 170 mm. of water.

In eight cases the spinal fluid contained a small number of red blood cells. In two cases there were large numbers of erythrocytes. There was no, or very mild, increase in the number of white blood cells.

In four cases the protein was above 130 mg. per 100 c.c. In the remaining cases, it was either normal or only slightly elevated.

Renal Changes: Signs and symptoms of impaired renal function were present in all cases. Repeated urinalyses disclosed albumin and casts in the majority of the cases. In only one case were there signs of hematuria.

The blood urea nitrogen was in some cases moderately elevated. Only in three cases were there found levels above 100 mg. per 100 c.c.

At autopsy the kidneys disclosed changes described as arteriolar nephrosclerosis in various stages of development. In but three cases were there changes characteristic of accelerated nephrosclerosis. In one instance the diagnosis of chronic glomerulonephritis was made, and in another instance the diagnosis of chronic pyelonephritis was made.

Cardiac Changes: Clinical and pathologic studies of the heart showed, in all but one case, signs of hypertrophy and dilatation of the left ventricle.

Previous Attacks: A history of previous attacks was obtained in only four cases. Some of the attacks were transient "strokes"; others consisted of "dizziness" or transient loss of speech.

Summary and Conclusions

Attention is directed to an acute form of hypertensive brain disease with characteristic clinical and pathologic manifestations observed in a series of 12 cases.

The clinical picture is characterized by sudden onset and rapid progression of severe headache, drowsiness, confusion, restlessness and delirium, accompanied by signs of increased intracranial pressure, such as elevation of spinal fluid pressure and papilledema.

The gross and histologic examination disclosed in all cases findings characteristic of cerebral swelling.

The clinical picture presented is analyzed and discussed, and the rôle of cerebral swelling in the production of the acute clinical syndrome is emphasized.

It is proposed to designate the clinicopathologic syndrome as "hypertensive cerebral swelling," and to consider it as an acute form of hypertensive brain disease.

The view is expressed that cerebral swelling is caused by acute vasomotor disturbances, followed by vasoparalytic distention of the veins and capillaries and associated with increased permeability of the vessel walls for serous fluid.

Early recognition of the syndrome is of paramount importance because of the reversibility of the early stage of cerebral swelling.

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CASE REPORTS

TREATMENT OF PNEUMOCOCCAL MENINGITIS WITH SULFADIAZINE AND INTRATHECAL PENICILLIN G WITH RECOVERY *

By GARFIELD S. BARNET, M.D.† *Aspinwall, Pennsylvania*

PRIOR to the advent of chemotherapy, pneumococcal meningitis carried mortality of almost 100 per cent.[1, 7] Sulfonamides lowered this depressing figure to some extent.[3] Recent minimum mortality figures representing the results of combined sulfonamide and penicillin therapy approximate 40 per cent.[4]

The present case report was deemed worthwhile because of the following features:

(1) The progression of meningitis during the administration of intramuscular and intravenous penicillin.

(2) The exclusive use of crystalline penicillin G for intrathecal administration in concentrated solution without adverse reaction.

CASE REPORT

A 23 year old married colored laborer noted the onset of headache, fever, vomiting, and generalized aching pain, associated with a chilly feeling March 10, 1947. He later developed right pleuritic pain with increased fever and prostration. Symptomatic treatment provided no relief, he became progressively worse, and was referred to the Veterans Administration Hospital, Aspinwall, Pennsylvania on March 15, 1947. At the time of entry physical findings were as follows: Temperature 102.8° (R), respirations 40 per minute, pulse 140 per minute. Blood pressure 88 mm. Hg systolic and 58 mm. diastolic. The patient was acutely ill, well nourished, and showed grunting respiration with dilatation of the nostrils, slight drowsiness, and marked dehydration. Decreased expansion of the right chest was apparent; there were scattered inspiratory râles, bronchial breathing, and dullness over the entire right chest, most marked over the anterior lung field. There was no abdominal distention or nuchal rigidity. The abdominal and cremasteric reflexes were present, the Babinski was negative, but the ankle and knee jerks were absent.

Course. The blood pressure returned to normal limits within a few hours following intravenous infusions of glucose in saline. The patient was placed in an oxygen tent and given 100,000 units of penicillin intravenously. Blood culture showed 350 colonies of pneumococcus per c.c. Serologic tests for syphilis were negative. The initial white blood count was 8,300; differential—polymorphonuclears 97 per cent (metamyelocytes 6 per cent, juveniles 30 per cent, band forms 55 per cent, segmented 6 per cent), lymphocytes 3 per cent, moderate toxic granulation. The red blood count

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† Resident, Internal Medicine. The resident training program at the Veterans Administration Hospital, Aspinwall, Pa., is under the supervision of the Dean's Committee, School of Medicine, University of Pittsburgh.

was 4,750,000; hemoglobin 14.5 gm. Urinalysis was normal except for 1 + albumin and 8 to 10 red cells per h.p.f. General measures included fluid intake of at least 3,000 c.c. daily, oxygen, vitamin B parenterally, and vitamin C. Oral fluids were supplemented by frequent infusions. Specific therapy was as follows: Penicillin, 50,000 units every three hours intramuscularly from March 15 to April 1. Booster injections of 100,000 units of penicillin were given intravenously twice daily from March 15 to March 24 inclusive.

For three days signs of consolidation persisted over the entire right lung, and the rectal temperature varied from 101° to 103.4° F. Two days after admission the white blood count was 11,400; polymorphonuclears 73 per cent, lymphocytes 20 per cent, monocytes 2 per cent, eosinophiles 5 per cent. There was progressive drowsiness, and on the third day of hospitalization the lower abdominal reflexes and cremasteric reflexes were absent, and the knee jerks could not be elicited. There was marked nuchal rigidity, and the Brudzinski sign was positive. Lumbar puncture revealed cloudy fluid under increased pressure with 1,647 white blood cells per cu. mm. (100 per cent polymorphonuclears). The globulin test was markedly positive. Smear was negative for bacteria, and culture was sterile on a medium containing penicillinase. Oral sulfadiazine was initiated in a dose of 4 gm. March 18, and 1 gm. was given every three hours thereafter with equal parts of sodium bicarbonate until March 27 inclusive. Crystalline penicillin G was administered intrathecally twice daily March 18 and March 19 in doses of 20,000 units and once daily March 20, 21, 22, and 24. Twenty-four hours following the institution of the above therapy, the spinal fluid was under increased pressure and contained 1,117 white blood cells per cu. mm. (100 per cent polymorphonuclears). The spinal fluid sulfadiazine level was 5 mg. per cent. Rectal temperature was 101° F.; the pulse rate averaged about 100. On the following day the spinal fluid appeared grossly clear and contained 504 white blood cells per cu. mm. (100 per cent polymorphonuclears). The globulin test was moderately positive. Blood culture taken at this time was sterile (the medium contained both penicillinase and para-aminobenzoic acid). The patient appeared mentally alert for the first time, and his pulse was of good quality. On the next day the spinal fluid contained 99 white blood cells per cu. mm. (100 per cent polymorphonuclears), and the globulin test was still moderately positive. The rectal temperature averaged 101.2° F. There were now patchy areas of consolidation in the right lung with coarse râles of resolution. Slight neck stiffness was present, the abdominal reflexes were present, and the Brudzinski was negative. The patient appeared very alert and generally much improved. Urinalysis was now normal. One week after admission the lung revealed increasing evidences of slow resolution, the spinal fluid contained 49 white blood cells per cu. mm. (100 per cent polymorphonuclears), and the globulin test was only slightly positive. The patient was out of the oxygen tent for long intervals, was taking fluids well, and appeared quite comfortable. On the ninth hospital day the spinal fluid was clear, under normal pressure, and contained three white blood cells per cu. mm. The globulin test was negative. Thoracentesis in the eighth and ninth interspaces yielded only 3 c.c. of serous yellow fluid. Physical signs were consistent with patchy consolidation and areas of atelectasis in the right lung. Neurological examination was normal. The temperature continued to drop by lysis until March 30 from which point it remained normal. Serial chest roentgenograms revealed slow progressive resolution with marked pleural reaction. There was elevation of the right diaphragm but no mediastinal shift. Chest roentgenogram April 24 revealed complete clearing of the right lung field but persistent elevation of the right diaphragm. On this date the patient was asymptomatic and gaining weight. Repeated urinalyses were normal. The patient developed a hypochromic anemia with red blood counts varying between 3,430,000 and 3,840,000 cells per cu. mm. and hemoglobin varying between 11 and 13 gm. The

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TABLE I

Date	Max. Temp.	Max. Pulse	Max. Resp.	WBC and Blood Culture	Spinal Fluid	Neurological	Treatment			
							Penicillin			Sulfadiazine
							I.M.	I.V.	I.T.*	
3/15	103.8° (R)	120	42	8,300 P—97 L—3 Toxic granulation 350 colonies pneumococcus per c.c.	—	Slight drowsiness, absent Achilles and knee jerks	50,000 U. every 3 hrs.	100,000 U. b.i.d.	—	—
3/16	101.4° (R)	120	48	—	—	—	50,000 U. every 3 hrs.	100,000 U. b.i.d.	—	—
3/17	102° (R)	90	40	11,400 P—73 L—20 M—2 E—5	—	Increasing drowsiness	50,000 U. every 3 hrs.	100,000 U. b.i.d.	—	—
3/18	103° (R)	98	35	—	1,647 cells/cu. mm. Globulin markedly positive. Pressure increased. Culture sterile	Stupor; positive Kernig and Brudzinski. Absent cremasteric and lower abdominal reflexes	50,000 U. every 3 hrs.	100,000 U. b.i.d.	20,000 U. b.i.d.	4 gm. stat initially and 1 gm. every 3 hrs.
3/19	101.5° (R)	105	30	17,000	1,117 cells/cu. mm. 100% polys. Sulfadiazine level 5 gm. %	No change	50,000 U. every 3 hrs.	100,000 U. b.i.d.	20,000 U. b.i.d.	1 gm. every 3 hrs.

TABLE I—*Continued*

Date	Max. Temp.	Max. Pulse	Max. Resp.	WBC and Blood Culture	Spinal Fluid	Neurological	Treatment			
							Penicillin			Sulfadiazine
							I.M.	I.V.	I.T.*	
3/20	101° (R)	105	28	Blood culture negative	504 cells/cu. mm. 100% polys. Globulin moderately positive. Grossly clear	Mentally clearer	50,000 U. every 3 hrs.	100,000 U. b.i.d.	20,000 U.	1 gm. every 3 hrs.
3/21	101.6° (R)	105	24	12,900 P—81 L—18 E—1	99 cells/cu. mm. 100% polys. Globulin moderately positive	Slight nuchal rigidity. Abdominal reflexes present. Brudzinski negative. Patient alert	50,000 U. every 3 hrs.	100,000 U. b.i.d.	20,000 U.	1 gm. every 3 hrs.
3/22	101.2° (R)	105	26	—	49 cells/cu. mm. 100% polys. Globulin slightly positive	No nuchal rigidity	50,000 U. every 3 hrs.	100,000 U. b.i.d.	20,000 U.	1 gm. every 3 hrs.
3/23	100.6° (oral)	100	28	—	Not done	No change	50,000 U. every 3 hrs.	100,000 U. b.i.d.	None	1 gm. every 3 hrs.
3/24	100.4° (oral)	100	40	—	3 cells/cu. mm. Globulin negative. Pressure normal	Normal	50,000 U. every 3 hrs.	100,000 U. b.i.d.	20,000 U.	1 gm. every 3 hrs.
	Temperature dropped by lysis and remained normal after 3/30				No further lumbar punctures performed	Remained normal thereafter	Continued until 4/1 incl.	100,000 U. 3/25 and 3/26	No further treatment	Continued to 3/27 incl.
						Totals:	6,800,000	2,100,000	160,000	80 gm.

* Intrathecal Penicillin G.

patient was discharged April 26, 1947 with instructions to take ferrous sulfate, 3 grains, three times daily.

The sequence of events and treatment are summarized in table 1.

Discussion

Price and Hodges [5] question the necessity for the intrathecal administration of penicillin and report two recoveries from pneumococcal meningitis using only the intramuscular and intravenous routes. However, the meninges are relatively impermeable to penicillin. After the parenteral administration of 100,000 units in normal individuals and in patients with meningitis, traces of penicillin are found in the spinal fluid for only brief periods.[6, 8] In contrast, the spinal fluid titer remains high 24 hours after intrathecal injection.[8] Consequently, many authors consider the intrathecal route essential.[6, 2, 8, 9]

In retrospect, the areflexia of the lower extremities and the drowsiness noted at the time of hospital admission in this case probably indicated early meningeal involvement. Despite the administration of penicillin, 50,000 units intramuscularly every three hours, and 100,000 units intravenously twice daily in an infusion, clinically recognizable meningitis ensued. This occurrence is in harmony with the conclusions of those authors favoring the use of intrathecal penicillin.

Sulfadiazine has been advocated in pneumococcal meningitis [6, 2, 4, 3] and was instituted as soon as the diagnosis was established. Booster doses of intravenous penicillin were employed because of the adverse prognostic significance of bacteremia,[7, 3] and in an attempt to eliminate the focus of infection.[7, 6] The administration of relatively large amounts of penicillin extrathecally will raise the spinal fluid concentration for periods up to one and one-half hours and thus might warrant less frequent intrathecal injections.[8]

Untoward reactions reported in cases receiving intrathecal penicillin by the lumbar route include neurogenic bladder and cauda equina disturbances,[9] transverse myelopathy.[1] Intraventricular injections have produced convulsions [6, 10] and vascular collapse.[10]

However in studies on normal human volunteers, spinal fluid pleocytosis, globulin rise, fever, and meningeal reaction were found to be minimized by careful technic.[2] The transverse myelopathy and neurogenic bladder could not be attributed unequivocably to penicillin, but occurred in patients treated for more than a week and/or receiving intrathecal doses of 40,000 units or more of penicillin daily. Intrathecal doses of 5,000 to 16,000 units every 24 hours will inhibit a standard strain of organism.[2, 6] In Sweet's series there was no correlation between dosage and survival rate.[9] Doses of 10,000 to 20,000 units intrathecally are well tolerated.[8, 2, 3, 6, 7] Sweeney and Leslie [11] injected 30,000 to 50,000 units by the ventricular and lumbar routes without ill effect. Rotman-Kavka et al.[12] report no untoward reactions from lumbar intrathecal injections of commercial penicillin, crystalline penicillin G and penicillin X, provided the doses were less than 100,000 units and the periods of injection less than six weeks. However, Smith, Duthie, and Cairns [6] believe that doses in excess of 20,000 units are not indicated.

Most investigators administer penicillin into the subarachnoid space in concentrations of 1,000 to 2,000 units per c.c.[7, 3, 6] This involves the injection of relatively large volumes of fluid which seems undesirable in the presence of

infection and greatly increases the risk of contamination.[6] Crystalline penicillin G is an effective agent against the pneumococcus.[4, 12] It was felt that this highly purified fraction might be better tolerated than the amorphous penicillin. Intrathecal injections of crystalline penicillin G in concentrations of 10,000 units per c.c. of physiological saline caused no adverse effect in this instance. The volume of injected material was greatly diminished. The rise in spinal fluid white count and globulin reported by Smith et al.[6] did not occur. The rapid therapeutic response recorded here is in accord with other reports which suggest that intrathecal penicillin is indicated in pneumococcal meningitis for periods of about five days in those cases demonstrating a good initial response.[6, 3]

Summary

1. A case of pneumococcal meningitis which developed during penicillin therapy of lobar pneumonia is presented, and the recent literature discussed.

2. Marked progression of the meningitis occurred until oral sulfadiazine and intrathecal penicillin G were administered, following which recovery ensued.

3. Crystalline penicillin G was injected intrathecally up to 20,000 units in relatively concentrated solution without adverse reaction, obviating large volumes of material and diminishing the risk of contamination.

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SYMPATHETIC PARALYSIS DUE TO METASTASIS AS INITIAL SIGN OF GASTRIC CARCINOMA *

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THE following case is of interest because the initial and, for almost two years, the only symptoms were those referable to a lesion involving the prevertebral thoracic sympathetic chain and adjacent intercostal nerves. Evidence of the metastatic nature of the lesion could not be found until a few months before death and autopsy alone showed that the stomach was the site of the primary tumor.

CASE REPORT

The patient, a 53 year old white male, was admitted to the U. S. Public Health Service Hospital, Lexington, Kentucky, on April 22, 1942, for treatment for drug addiction. The past medical history was essentially negative except for six attacks of "pneumonia" since 1928. The last episode occurred about March 25, 1942. Recovery was uneventful.

The present illness began about the time of his recovery from "pneumonia," in March 1942, when he began to have constant severe pain in the right breast. On June 12, 1942, he was admitted to the Neuropsychiatric Ward because of this complaint for which no local cause could be found. On questioning, the patient stated that the pain was "boring" or "stabbing," usually localized in the right nipple, although occasionally it seemed to originate in the right scapular region and radiate to the breast. Rarely it seemed to radiate to the right shoulder and down the inner aspect of the right arm to the elbow. It was aggravated by coughing, straining, sneezing and flexion of the neck.

Physical examination was negative except for persistent arterial hypertension (150 to 200 mm. Hg systolic, and 90 to 110 mm. diastolic) and early hypertensive changes in the retinal vessels. Repeated neurological examinations revealed only a mixture of hypalgesia and dysesthesia in the right D–4 to D–6 dermatomes. Urinalysis, blood counts, and repeated spinal fluid examinations with Queckenstedt tests gave results within normal limits. Blood and spinal fluid examinations were both negative for syphilis.

The Minor-Peet starch-iodine sweating test revealed anhidrosis of the right half of the face and neck, the right upper extremity and the right half of the chest down to about D–4. The presence of sympathetic paralysis was subsequently confirmed by a charcoal sweating test and plethysmographic studies. Because of the absence of miosis, ptosis and enophthalmos, it was evident that the lesions were localized between the first and fourth dorsal segments. Since there was no evidence of involvement of the spinal cord or of subarachnoid block, the lesion was considered to be extradural and probably extravertebral. Further evidence that peripheral nervous structures were involved was afforded by the histamine test described by Harris.[1] Approximately 0.1 c.c. of a 1:1000 aqueous solution of histamine phosphate was injected intracutaneously at intervals of about 2 cm. along the right axillary line in the vicinity of the fourth thoracic dermatome. Above the lower border of D–4 the local

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wheal was present but the flare failed to appear. Below D–4, the usual wheal, flare and pseudopod formations appeared promptly.

Because of these findings, the bony structures and the posterior mediastinum of the upper thorax were investigated carefully. However, roentgenograms of the chest and thoracic spine were reported to be negative. Fluoroscopic examination of the chest after swallowing a barium meal revealed no evidences of a local tumor. Intravenous and retrograde pyelograms revealed no evidence of hypernephroma or other renal tumor.

The patient's symptoms continued unabated until posterior rhizotomy of the first to the seventh dorsal roots on the right side was performed by Dr. J. P. Evans, consulting neurosurgeon, for the relief of pain. Following the operation, the patient had no further pain, gained weight, and required no medication. The findings on physical and neurological examinations were the same as before with the addition of anesthesia from the first to the seventh dorsal dermatomes on the right side due to the operation. In December, 1943, while doing some light work, his right leg suddenly gave way and he fell. This caused an extracapsular fracture of the neck of the femur. He was placed in traction and the fracture healed with good position of the fragments.

In February, 1944, he complained of return of the right scapular pains, of "gas on the stomach" and pains over the kidney areas. On March 2, 1944, roentgenograms of the chest, taken routinely during a clinical tuberculosis survey in the hospital, revealed evidence of destruction and cyst formation in the right fourth rib, near the spine. In April, 1944, a small irregular nodular mass was palpated over the lower left rectus muscle. Biopsy was performed and the specimen was reported to be that of a metastatic adenocarcinoma, source unknown. A gastrointestinal series was then performed and on fluoroscopy there appeared to be a retroperitoneal mass which deformed the outline of the duodenum and pyloric end of the stomach. The patient's condition became progressively worse with weight loss, multiple complaints of pain, and edema of the legs and scrotum. He became stuporous and died on May 17, 1944, approximately 26 months after the onset of his illness.

The clinical impression was that the patient had a retroperitoneal tumor with metastases to the right fourth rib and adjacent sympathetic trunk, and to the abdominal wall.

Pathological Findings

At autopsy a large irregular shaped tumor mass was found involving the posterior wall and lesser curvature of the stomach. The mass was fixed to the retroperitoneal tissues including the pancreas. The right paravertebral sympathetic chain was enmeshed in a dense fibrous tumor which occupied the right costovertebral angle and was adherent to the anthracotic right lung. This infiltrated the fourth rib and enmeshed the corresponding intercostal nerve (figure 1). Microscopic examination of the tumor in the wall of the stomach showed a carcinoma in which many of the cells were distended with mucus, forming typical signet ring cells. In other areas there was adenomatous arrangement of the cancer cells. The tumor tissue from the right costovertebral angle and from the decalcified rib showed an adenocarcinoma similar to that involving the stomach. Nerve trunks were found in the tumor involving the ribs and paravertebral spaces. There was extension of the cancer into the pancreas. The other pathological findings were not pertinent to this report.

The pathological diagnoses were: Massive adenocarcinoma of stomach (posterior wall and lesser curvature with extension to pancreas); metastatic carcinoma to right costovertebral area fourth rib and intercostal spaces (right), and subcutaneous tissue (lower right rectus muscle); hydronephrosis; lobular pneumonia; chronic passive congestion in liver, kidneys, and spleen; cardiac hypertrophy; atrophic changes in epithelium of thyroid; zones of liquefaction necrosis in left cerebral hemisphere (centrum ovale).

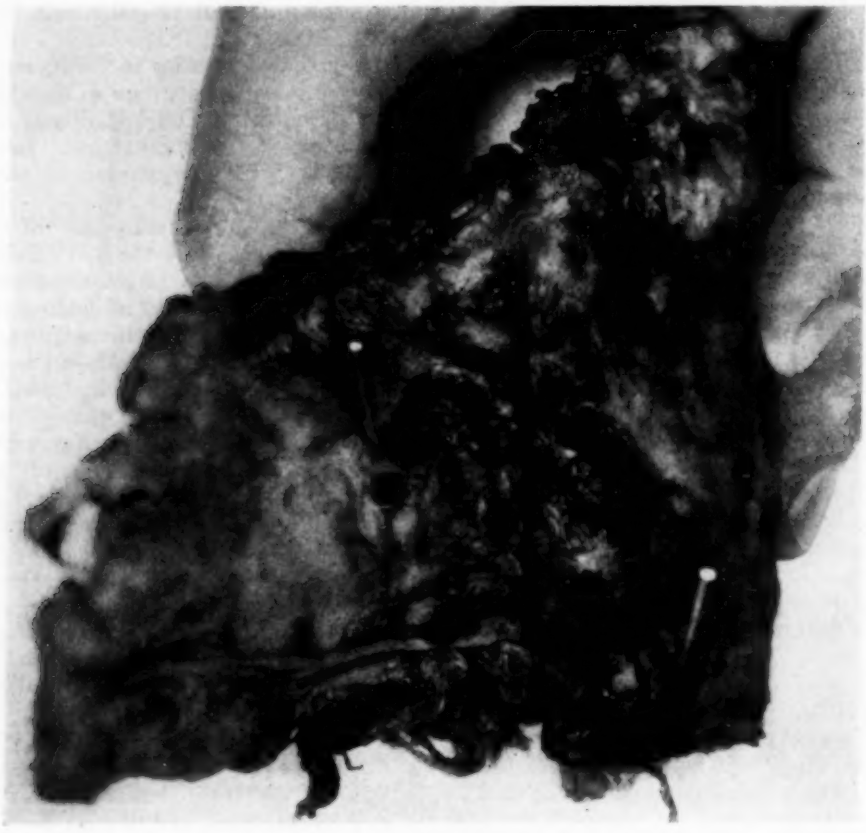

FIG. 1. Specimen showing metastatic tumor involving the right fourth costovertebral angle and corresponding intercostal nerves, with extension medially to involve the prevertebral sympathetic chain. The upper pin indicates the upper border of the tumor mass. The lower pin is placed in the sympathetic ganglionic chain.

COMMENT

The interesting feature of this case is the long interval (about two years) between the onset of symptoms due to metastasis and evidence of disease of the stomach, which was the site of the primary lesion. In this connection it may be emphasized that, where metastatic tumor is suspected, the gastrointestinal tract should be investigated even though there are no gastrointestinal symptoms. Whether or not the metastases involved the bony structures first and the nervous structures secondarily could not be determined with certainty. Bone metastasis as the initial sign of carcinoma of the stomach is rare but does occur occasionally.[2] However, the bulk of the metastatic tumor mass was found in the soft tissues about the prevertebral sympathetic chain and the adjacent intercostal spaces. Also, spot films of the bony structures which were subsequently involved were negative for at least one year after the onset of sympathetic paralysis. Therefore, it appears more probable that the prevertebral soft tissues with their nervous structures were invaded first by this metastatic tumor.

SUMMARY

1. A case is reported in which symptoms due to metastasis from carcinoma of the stomach to the prevertebral soft tissues, involving the sympathetic chain and adjacent intercostal nerves, antedated by about two years any symptoms or signs referable to the gastrointestinal tract.

2. It is emphasized that the possibility of carcinoma of the stomach should be investigated where the clinical evidence indicates a localized neoplastic lesion, even though there are no gastrointestinal complaints.

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PROGRESSIVE COCCIDIOIDOMYCOSIS: REPORT OF A CASE*

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THE purpose of this report is to present another case of progressive or disseminated coccidioidomycosis with clinical data and autopsy findings, together with a brief discussion of some aspects of the disease.

CASE REPORT

On January 4, 1946, a 24 year old white male was admitted to the Pasadena Regional Hospital, complaining of pain in his left chest, shortness of breath, marked fatigue, and bouts of chills and fever.

His illness dated back to August 1945 when he made two trips to the San Joaquin Valley driving a truck. He stayed there about one day each time. Approximately two weeks after the last trip, he developed constant frontal headaches, marked lassitude, and fever, and by September 10, 1945 had a fever as high as 104° F. with chills. He was hospitalized on September 11, 1945. Roentgenograms of the chest and malaria smears taken at this time were negative. Symptoms continued, and on or about October 10, 1945 he developed constant aching pains in the left chest and roentgenographic evidence of fluid in the left pleural space. An intradermal skin test with coccidioidin (1:100 dil.) was strongly positive. Blood specimens were sent to the laboratory of the coccidioidomycosis study of the Commission on Epidemiological Survey, Board for the Investigation of Epidemic Diseases, Preventive Medicine Service, Office of the Surgeon General at Stanford Medical School. The first sample, dated November 26, 1945, showed a positive complement fixation test up to a 1:8 dilution. A second sample, dated December 19, 1945, also was positive for complement fixation in a dilution of 1:8, but the precipitin test was now negative. The conclusions of this laboratory were that there had been no significant change in the titer of the antibodies and that stabilization of antibody production at this moderate level indicated that the infection was being well handled.

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Clinical records from this hospital were not available, but the patient stated that he received sulfadiazine, followed by penicillin, without improvement.

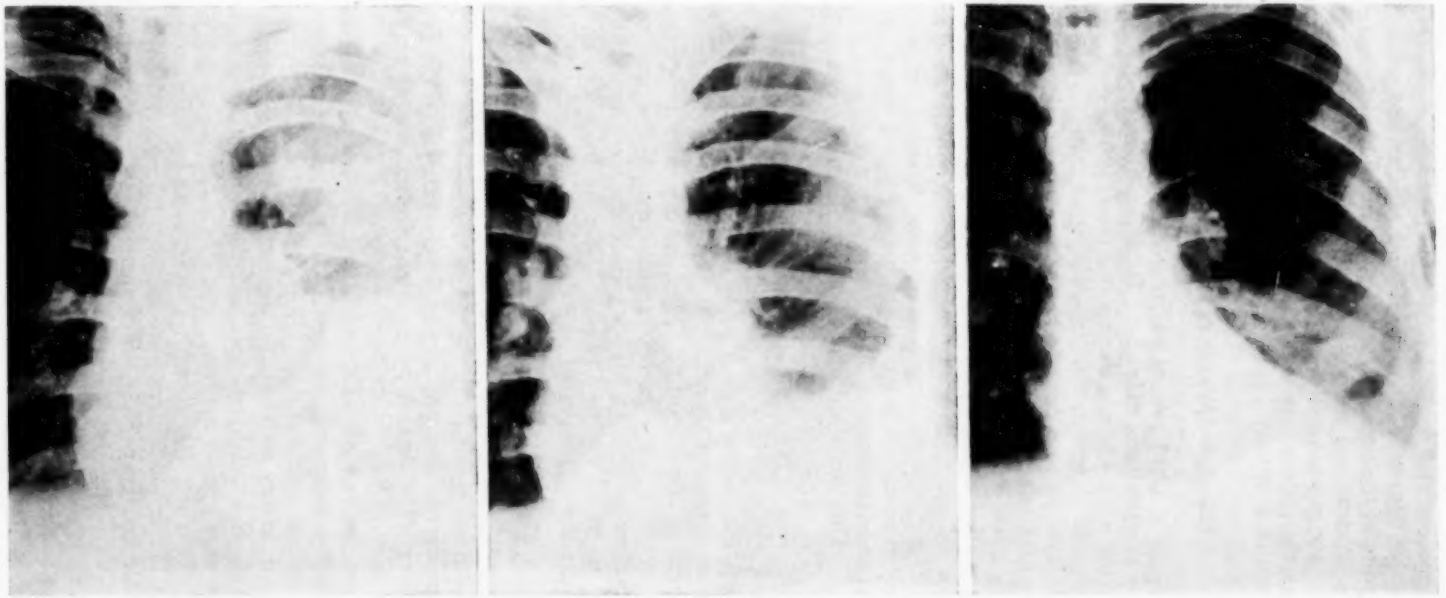
On January 4, 1946, the patient was transferred to the Pasadena Regional Hospital. Physical examination on admission revealed a well developed, poorly nourished, young, adult white male, who appeared chronically ill. Temperature on admission was 101° F., pulse 84 per minute, and respirations 24 per minute. There was diminished resonance over the entire left chest, with only faintly audible breath sounds over the same area. No râles were heard. There was moderate pallor of the mucous membranes. A complete hematologic examination showed a red cell count of 3.5 million, hemoglobin of 11 gm., and a white cell count of 4,750 with a differential of 62 per cent neutrophiles, 35 per cent lymphocytes and 3 per cent monocytes. The sedimentation rate was 11 mm. in 45 minutes (Osgood and Haskins modification of Westergren's method). The urine was normal. Roentgenogram of the chest showed an area of increased density obliterating the lower third of the left hemithorax and was believed to represent pleural thickening and effusion (figure 1a). There were very small areas of decreased density scattered through this area which resembled cavity formation. Skin tests with intradermal coccidioidin were repeatedly negative, using a 1:100 dilution. Tuberculin tests were positive with a 1:1000 and 1:100 dilution (one plus and two plus respectively). A blood sample sent to the laboratory of the coccidioidomycosis study of the Commission on Epidemiological Survey, Board for the Investigation of Epidemic Diseases, Preventive Medicine Service, Office of the Surgeon General at Stanford Medical School, revealed a positive complement fixation test in a 1:8 dilution. (The precipitin test could not be run because of contamination.) The conclusions of that laboratory were as follows: There has been no significant change in serology which is reassuring in view of clinical severity and apparent anergy. The latter is rather alarming (he previously had good reactivity).

Repeated gastric lavage specimens were negative for acid-fast bacilli, both by smear and culture. Blood culture planted on blood agar, brain heart infusion broth, and Sabouraud's glucose agar were repeatedly negative for bacteria and fungi. Aspirated pleural fluid failed to grow out any organisms on two occasions. No sputum was obtainable at any time.

Serial roentgenograms of the chest showed a slight clearing of the pleural effusion in the left lower chest (figures 1b and 1c), but otherwise no essential change. The right lung remained roentgenographically negative. Survey films of the long bones showed no abnormalities, and a flat plate of the abdomen was negative.

Hematologic studies revealed a persistent, mild hypochromic anemia, mild acceleration of the sedimentation rate, and mild leukopenia. The blood non-protein nitrogen, urea nitrogen and chlorides were within normal limits. The serum proteir was 5.2 gm. per 100 c.c. of blood, with an albumin of 2.8 gm. and a globulin of 2.4 gm.

Clinical Course: The patient's course was progressively downward. There was a constant temperature elevation which initially ranged from 99° F. to 102° F. to 104° F., and during the last two weeks of life, from 103° F. to 105° F. There was progressive weight loss, fatigue, and cachexia. The patient was given a course of penicillin therapy, and received a total of 6,260,000 units in doses of 40,000 units, then 60,000 units intramuscularly every three hours, with no clinical improvement nor effect on temperature. He was treated with repeated blood transfusions, intravenous glucose, plasma and physiological saline, and a high caloric, high vitamin diet. One hundred c.c. of amino acids were given intravenously three times daily, plus 12 mg. of vitamin K by mouth. On January 24, 1946, the patient first gave evidence of apparent involvement of the central nervous system, manifested by emotional disturbances, suicidal intent and generalized tremors. About one week later, he became delirious and incontinent of urine and feces. Respirations became shallower and more rapid, and the patient appeared to have respiratory distress, but was not cyanotic. On February 10,



(*a*) (*b*) (*c*)

FIG. 1. (*a*) Roentgen-ray film of chest dated January 4, 1946. Interpreted as pleural effusion and thickening. (*b*) January 26, 1946. Effusion clearing. (*c*) February 4, 1946. Some fluid remains in left costophrenic angle. Pulmonary lesion now shows up well.

the patient became stuporous and finally lapsed into coma. There were generalized body tremors, hyperactive deep reflexes with bilateral patellar and ankle clonus, and there was marked rigidity of the neck. A spinal puncture showed a clear fluid under no increased pressure. Smear and culture revealed no organisms. There were six leukocytes per cu. mm.; the glucose and protein values of the spinal fluid were normal. Two days before death the abdomen became distended, and the patient became jaundiced. The patient died on February 13, 1946 at 0245, following a spell of vomiting.

Necropsy Report (Condensed)

A. Gross: Lungs. The right pleural cavity contained about 50 c.c. of blood-tinted fluid; the left was completely obliterated by dense fibrous adhesions. In the upper medial aspect of the left lower lobe there was a rounded firm node measuring 1.8 by 1.6 by 1.2 cm., composed of semicaseous, greenish-gray material and delimited by a dense dark red-gray layer up to 3 mm. thick. A smaller node, 7 mm. in diameter, was located below the first, which it resembled except that it was not well delimited and was surrounded by a few scattered pinhead size nodules. The cut surfaces of the lung in general were mottled uniformly by many tiny pinpoint size translucent gray nodules, and were dark red and moist with frothy fluid. The right lung answered to a similar description except that no larger nodes were found. The mucosa of the bronchi was moderately injected. A few tracheobronchial lymph nodes were enlarged to a lima bean size and were semicaseous.

Peritoneal Cavity. This contained about 500 c.c. of cloudy yellow fluid mixed with flakes of fibrin. The peritoneal surfaces were covered with patchy membranes of fibrin, especially the serosa of the small intestine. The greater omentum was thickened and indurated, and its cut surface was mottled by irregular grayish patches. The surface of the liver was covered by a thick layer of gray-yellow exudate.

Spleen. The spleen weighed 400 grams. It was surrounded by fibrinous exudate and was partly adherent to the diaphragm. The capsule was dark purple-red and studded by irregular grayish yellow nodes varying from a few mm. to 2 cm. in diameter. The cut surfaces presented a similar picture and were mottled by numerous large and small nodes up to 2.5 cm. in diameter. Some of the nodes on the capsule were semiliquid and partially disintegrated, and the necrotic material had spread into the peritoneal cavity.

Liver. The liver weighed 1600 grams. The capsule was covered with a thick layer of grayish-yellow caseous and fibrinous exudate, and was studded by scattered nodes which resembled those described in the spleen. Some of the nodes had broken down and the necrotic material was continuous with the exudate on the surface. The cut surfaces of the liver were studded by occasional nodes similar to those in the spleen.

Pancreas. The pancreas weighed 120 grams, and was normally firm and lobular. A few peripancreatic lymph nodes were enlarged to navy bean size and were composed of pale gray-yellow semicaseous tissue.

Kidneys. The right kidney weighed 200 grams, and the left kidney 180 grams. The cortex was grayish red and hyperemic, and the differentiation was only fair. Otherwise the kidneys were grossly normal.

Brain. The brain weighed 1600 grams. There was an increased amount of clear intermeningeal fluid. The leptomeninges were thin and transparent. The cortex and basal ganglia were pale and gray. The white matter was edematous and injected. The lateral ventricles were slightly dilated with clear fluid and the ependyma was smooth.

B. Microscopic: Lungs. The large node described above in the lower lobe of the left lung consisted of finely granular, eosinophilic, caseous, necrotic material sur-

rounded by a thin, partly hyalinized fibrous capsule. It lay near the pleural surface from which it was separated by a thin rim of compressed atelectatic lung. Adjacent to the large nodule and scattered through the lung were many smaller, similar areas of necrosis. There were occasional Langhans' giant cells and doubly-contoured coccidioidal spherules in the granulomatous tissue surrounding these caseous areas. Some of the smaller foci were in an early stage of development and showed a small central area of suppuration containing polymorphonuclear leukocytes and granular, necrotic tissue debris surrounded by a hyaline change in the fibrous stroma. The older lesions were larger, showed a granulomatous reaction, and the cellular infiltrate consisted mainly of lymphocytes and plasma cells, with a few epithelioid cells and giant cells toward the middle. The largest lesions had a caseous center. Many *Coccidioides immitis* organisms were seen in and around the various lesions, most of which were in the spherule stage, but a few were enlarged and showed endospore formation. Between these foci of infection, the lung parenchyma showed edema, atelectasis, blood in the alveoli, hemosiderin ingestion by macrophages and patchy areas of fibrosis and lymphocytic infiltration. The pleura contained small nodules of granuloma and also was diffusely thickened with granulation tissue.

Tracheobronchial nodes. These were filled with large areas of caseous necrosis surrounded by fibroblastic proliferation containing giant cells, plasma cells and lymphocytes, though occasionally polymorphonuclear leukocytes predominated. Numerous organisms were seen in the latter areas.

Liver. There were numerous foci of caseous necrosis surrounded by granulomatous tissue. Many *Coccidioides immitis* spherules and large endosporulating forms were seen along with numerous giant cells. In addition, there were large confluent areas of suppuration and tissue necrosis in which the polymorphonuclear leukocytes predominated, and numerous organisms were seen. Around these foci there was as yet little fibrous proliferation.

Spleen. This presented a picture similar to that of the liver but with a relatively greater amount of acute necrotic suppurative reaction than of granuloma production.

Kidneys. One small area of necrosis and suppuration was seen, with both sporulating and non-sporulating types of organisms. Elsewhere there were small foci of fibroblastic proliferation infiltrated with plasma cells and a few polymorphonuclear leukocytes. Interstitial hyperemia was present.

Brain. This showed edema, hyperemia and focal areas of pyramidal cell degeneration. The white matter was edematous and hyperemic. The meninges were normal in appearance.

Case Comment

This case of progressive coccidioidomycosis had several instructive features. The history indicates how a short contact with the infected dust can give rise to the severe disseminated infection. The patient was a white person, in whom the progressive form of the disease appears to be much less common than in colored races.[16, 20] Stabilization of antibody production at a moderate level was misleading in that such a finding often indicates that the infection is being adequately localized by the immune forces of the body (see laboratory report above). The development of skin energy to coccidioidin in the disseminated stage of coccidioidomycosis, together with the positive tuberculin test, as seen in this case, is a combination for clinicians to guard against, lest they interpret this as indicating the presence of active tuberculosis and the absence of coccidioidal infection. The converse of this picture might also occur in endemic coccidioidal areas in a patient with miliary tuberculosis. In both diseases, so similar clinically and

roentgenographically, the disseminated form frequently is associated with skin anergy.[5, 6, 16, 20]

The presence of a large, subpleural caseous nodule in the left lung with caseation of the tracheobronchial lymph nodes suggests a primary infection closely analogous to the primary tuberculous complex of Ranke with the Ghon tubercle.* The subsequent lymphatic and hematogenous spread to the abdominal organs and remaining lung tissue presumably took place in a manner analogous to that of miliary or disseminated tuberculosis.

Coccidioidomycosis of the peritoneum occurs in the disseminated disease by hematogenous spread as does tuberculosis of the peritoneum in miliary tuberculosis.[20] In this case there was an acute, generalized, exudative peritonitis due to intraperitoneal rupture of caseous liquefying nodules on the surface of the spleen and liver, analogous to a generalized tuberculous peritonitis.[17]

Coccidioidal meningitis is a common terminal feature of the disseminated form of the disease, especially in the white race.[1, 2, 6, 16, 20] Abbott and Cutler [1] believe that it occurs in about 25 per cent of fatal cases, while Ash and Spitz [2] feel that it is even more common. The symptoms in this case were due to diffuse parenchymal damage to the central nervous system rather than meningitis, although the signs were suggestive of the latter condition. Failure to isolate the organisms from the spinal fluid is frequent even in frank cases of meningitis. The colloidal gold curve is often of the paretic or first zone type and the cell count varies from 50 to 200 cells per cu. mm. with about 75 per cent lymphocytes.[1, 18]

Penicillin was used in doses of from 40,000 to 60,000 units intramuscularly every three hours up to a total of 6,260,000 units, with no demonstrable effect on the clinical course. Michael et al.[18] have previously reported a penicillin failure using a total of 3,081,000 units.

Discussion

The concept of coccidioidomycosis has undergone considerable change since the first case reports. These early workers believed it to be a rare protozoan infestation.[19, 25] When the etiologic agent became known the disease was thought to be an uncommon, highly fatal fungus infection.[4, 7] It is now recognized as a common (in endemic areas), usually benign, pulmonary reaction to the inhalation of infective dust, self-limited and often subclinical, but which may resemble a common "cold" or the "flu" for which it is frequently mistaken.[4, 5, 6, 8, 9, 16, 20]

Etiology. The etiological agent, *Coccidioides immitis,* appears in two forms, one on culture media and one in the tissues of the animal host. The tissue or parasitic phase is a protoplasmic spherule with a thick, doubly contoured wall, and measures 10 to 60 mu. in diameter. As this spherule becomes larger, it develops 50 to 100 endospores which break out of the capsule and repeat the process. In the saprophytic phase, the organism develops on a variety of media as a mould-like growth with the production of a white, cottony, aerial mycelium, which turns tan with age. Microscopically the mycelium consists of branching septate hyphae, which later become segmented into oblong or rounded spores

* Butt and Hoffman [4] observed healed calcified primary pulmonary lesions of coccidioidomycosis at autopsy and reported that they were indistinguishable from those of calcified primary tuberculosis.

(arthrospores). These spores are the highly infective form of the organism and are found in the dusts of endemic areas.[5, 6, 8, 9, 16, 20]

Geographic Distribution. By means of the skin test, Army medical personnel have outlined endemic areas in the southwestern United States, including the great central valley of California north to Madera, the western slope of the Coastal Range, all of Arizona and New Mexico, southern Utah, southern Nevada, west Texas, and northern Mexico. Isolated cases have been reported in northern, central and eastern United States. Hawaii has been implicated as well as the Chaco region of Argentina and Uruguay.[20, 25] Smith feels that the arid regions of the Near East, Mongolia and Australia also deserve further investigation.[20]

Epidemiology. The cause of the endemicity has been in doubt. There is no evidence of direct patient to patient infection. The organism has been isolated from the soil in endemic areas, but with difficulty owing to a sparse, highly spotty distribution.[10] Because of these facts, Emmons was led to look for an animal reservoir which he believes he has found in the wild rodent population of endemic areas.[10, 11, 12] He suggests examination and culture of lungs from samples of the rodent population as a quick, dependable method for determining the presence or absence of *Coccidioides immitis* in a specific locality. If valid, this method has a theoretical advantage over the skin test in that it is a more direct measure of an infective area, and therefore will be more sharply delineative, whereas the skin test, which is indirect, will be influenced by migration of the inhabitants of the region. Dickson,[8] Dickson and Clifford [9] were among the first to recognize the fact that there was a common, benign form of coccidioidomycosis, and that the disease known as "San Joaquin," "Desert," or "Valley" fever was the primary coccidioidal infection accompanied by erythema nodosum. This skin phenomenon is seen in 3 to 5 per cent of the cases and is believed to be a hypersensitive manifestation of a freshly acquired allergy.[20, 21] The allergy is of long duration and appears to confer lasting immunity to a second similar infection and to the progressive form of the disease as well.[16, 20, 21] In the San Joaquin Valley, Smith [21] found a seasonal variation in "Valley" fever with a peak in the dusty fall and a low incidence in the wet winter. He also observed that this manifestation is most common in white females and in newcomers to the region. Four-fifths of the long time residents in the Southern San Joaquin Valley give a positive coccidioidin skin test.[20, 21] There is a higher incidence (four to seven times) of progressive coccidioidomycosis in males and there is marked predilection of the disseminated form for the dark-skinned races, e.g., Filipinos, Negroes and Mexicans.[2, 6, 20, 21]

Pathogenesis. In most cases, infection is caused by inhalation of dust containing infective arthrospores. Dusty objects such as hay, clothes, camping equipment, etc., when carried from an endemic area, can infect persons in remote noninfected areas. Rarely the skin is the portal of entry.

Pathology and Roentgenographic Findings. The majority of infections are benign and self-limited; therefore, early human pathological material is lacking. Dickson and Clifford [9] report that guinea pigs and rabbits forced to inhale the spores, develop a transient interstitial pneumonitis, which shows the same hilar and parenchymal shadows on the roentgenogram as does the primary infection in humans. According to these workers, the initial reaction is an irritation of the lymphatics which does not cause necrosis or granuloma production. Clark and Gilmore [5] feel that the initial pulmonary infiltration associated with the pri-

mary infection has a distinctive roentgenographic pattern by which it may be differentiated from early adult tuberculosis. They stress the relatively marked hilar or mediastinal adenopathy in primary coccidioidomycosis which is lacking in adult (superinfection type) tuberculosis. The roentgenographic picture, however, is frequently indistinguishable from bronchopneumonia or primary tuberculosis, and at times the sharp outline of the shadow suggests metastatic malignancy.[16, 20] The lung infiltrations often disappear entirely but may occasionally leave fibrosis as a round or linear scar.[5] Reinfection apparently seldom occurs. In more severe pulmonary involvement, there may be an extensive caseous pneumonia, perhaps with cavity formation. However, even these extensive pathological changes, which would give a grave prognosis in tuberculosis, tend to resolve completely on bed rest and other supportive measures.[5, 6, 16, 20] The progressive form of the disease may come after widespread lung involvement, or may originate from a relatively small focus. The symptoms are referable to organs showing massive lesions, especially lungs, bones, lymph nodes, meninges and occasionally skin. Clinically, by roentgen-ray, and in anatomic distribution, the visceral lesions may closely resemble tuberculosis, blastomycosis, or one of the lymphomas.[2] Subcutaneous and multiple "cold" abscesses seem to be more frequent in coccidioidomycosis than tuberculosis.[20]

Histologically the early lesions are mostly purulent with some necrosis, surrounded by plasma cells, lymphocytes, a few monocytes and connective tissue showing hyaline change. The older lesions are granulomatous, containing epithelioid and giant cells and frequent caseation. The healing or healed stage consists of replacement by a fibrous scar and sometimes eventual calcification.[2] Areas containing many organisms, both sporulating and non-sporulating, may present a more acute suppurative and necrotic picture, whereas areas with only a few organisms show chronic granuloma production (figure 2). The non-sporulating spherule of *Coccidioides immitis* is practically indistinguishable from the non-budding form of *Blastomyces dermatitidis*, and animal inoculation may be necessary in cases of doubt.[2, 6, 20]

Immunology. A specific soluble substance was found in liquid cultures of *Coccidioides immitis* by Hirsch and Benson [14] which gave reliable positive skin tests in infected animals and humans. This substance is dialyzable, relatively heat stable, and is probably a polysaccharide.[23] It has been standardized in skin test units [23] and has been shown to give no cross reactions in cases of tuberculosis [15] or blastomycosis.[4] Sensitivity to coccidioidin usually develops 10 days to one and one-half months after acquiring infection.[20] Butt and Hoffman [4] feel that the intradermal coccidioidin skin test has the same clinical significance as the intradermal tuberculin test, but Stewart and Kimura [23] warn that the skin test should not be regarded as absolutely specific until the antigenic cross relations and the generic position of the organism are established. Skin test with coccidioidin in the Middle West and a few Eastern states have shown some doubtful and some definite positives which may be due to cross reactions with other fungus disease.[20] Histoplasmosis is endemic in the Middle West. Emmons and Ashburn [12] believe that *Coccidioides immitis* and *Haplosporangium parvum* are antigenically related, although they found that experimental Haplosporangium infection in mice did not protect against subsequent infection with *Coccidioides immitis*.[3] Regardless of theoretical objections, the skin test is widely used as a practical, clinical and epidemiological procedure.

Serological studies have also proved valuable. The complement fixation and precipitin reactions have been employed and appear to correspond, in a general way, to the extent of the disease process. Thus, the mildest cases usually show no demonstrable antibody production.[6, 20] The more severe, but still localized cases, often show a rise in precipitins which may fall as the complement fixation titer rises. Precipitins are poorly demonstrated in most disseminated infections,

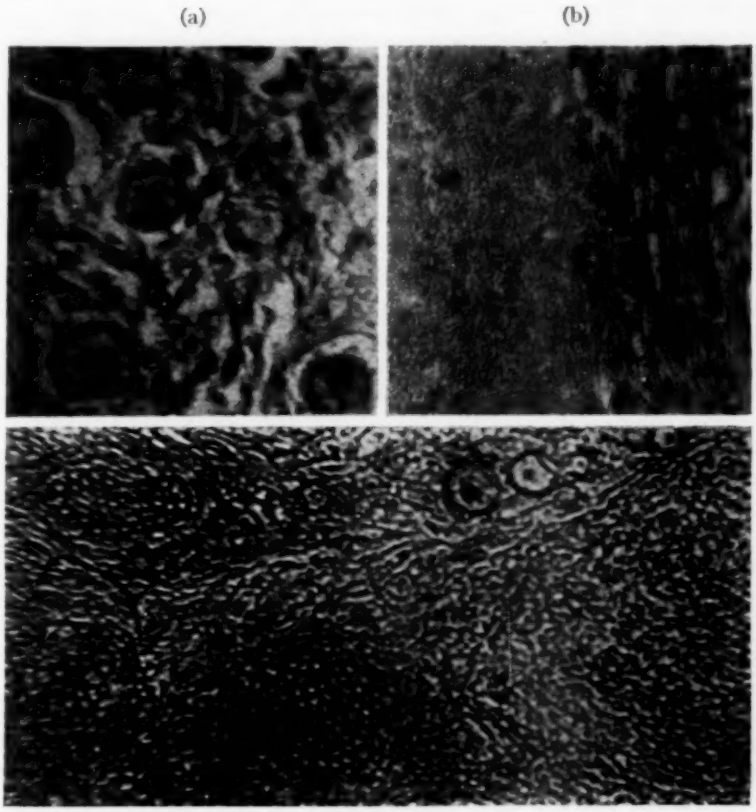


FIG. 2. (*a*) Spherule stage of *Coccidioides immitis*, tracheobronchial lymph node. × 450. (*b*) Edge of caseated area, tracheobronchial lymph node. × 400. (*c*) Spleen, numerous endosporulating organisms, with acute necrotic reaction. × 350

probably because precipitins are generally transient and dissemination usually occurs later in the course of the disease, at which time the precipitins may have already disappeared. When healing occurs (as in the vast majority of instances), the complement fixation falls. The precipitins may remain high for a time but usually disappear before the complement fixing antibodies. A rising, or persistently high complement fixation test, is usually interpreted as indicative of dissemination.[20, 22] In some disseminated cases, fixation of complement may occur completely even in dilutions up to 1:256 or higher.[20] Dr. C. E. Smith of Stanford University feels that no hard and fast rules for the interpretation of serological tests can be set because there is such an individual variation in anti-

body response, and urges that serologic data be closely correlated with clinical findings.[22]

Therapy. There appears to be no specific therapy as yet. Penicillin was given in this case with no demonstrable effect, and Michael et al.[18] reported a failure with 3,081,000 units.* Sulfonamides have been found useless. Arsphenamine, iodides, gentian violet, etc., have all been tried without beneficial effect.[16, 20] Desensitization to coccidioidin along with injections of colloidal copper were tried by one worker with promising results.[6] Goldstein and McDonald [13] report a possible therapeutic success in one case using transfusions of convalescent blood but admit that no conclusions could be drawn from one case. Smith [22] has tried similar "immunotransfusions" with no favorable results and feels that ordinary transfusions may be just as beneficial. Salicylates are useful in the hyperergic type of primary infection with erythema nodosum and painful joints.[20] Bed rest and conservative supportive therapy will cure most cases of primary pulmonary infection, even with large cavity formation.[6, 16, 20] Collapse therapy is occasionally necessary, and artificial pneumothorax is preferable to the major procedures. Once dissemination has occurred the prognosis is rather poor, depending of course upon the sites of dissemination, with about a 50 per cent fatality rate. Smith [20] believes that strain difference in the organism is not responsible for the variation in severity of infection, but that such variation is apparently dependent upon racial, sexual, familial and individual factors, as well as the inoculating dose of the organism. Efforts should be made as early as possible to give rest and general supportive treatment to assist the patient in focalizing the infection.

Summary

A case of progressive coccidioidomycosis is presented with clinical data and necropsy findings. A generalized coccidioidal peritonitis found at autopsy was apparently caused by the intraperitoneal release of infective material from necrotic liquefying nodules on the surface of the spleen and liver. The complement fixing antibodies never gave a positive test in dilutions greater than 1 : 8, and the patient became anergic to intradermal injections of coccidioidin (1 : 100 dil.) in the terminal stages of the disease. A total of 6,260,000 units of penicillin was given with no demonstrably beneficial clinical effect. Many analogies can be drawn between coccidioidomycosis and tuberculosis. A brief discussion of some aspects of the disease is presented.

Acknowledgment

The writer wishes to acknowledge his gratitude to Dr. C. E. Smith, Stanford University Medical School, for his helpful suggestions and criticisms. I should also like to thank Miss Ann M. Olson who typed the manuscript, and William Woody, Hospital Photographer, who helped prepare the photographs.

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* Tager [24] found that penicillin did not inhibit the growth of *Coccidioides immitis* in vitro.

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PULMONARY ASPERGILLOSIS: REPORT OF TWO CASES *

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A VARIETY of symptoms and roentgenographic changes have been reported as indicative of pulmonary aspergillosis. This suggests that there may be considerable variation in the individual response of the host to the invading microörganism. Cases of primary and uncomplicated pulmonary aspergillosis have been described which by their course and roentgen-ray appearance simulated tuberculosis [1, 2] whereas others behaved like an acute lobar pneumonia.[3]

In the two cases to be reported an aspergillus was the sole or predominant infective agent. Symptomatically and in roentgen-ray appearance, however, these cases differ markedly. This emphasizes the dissimilarity of signs one may encounter in this disease.

Case 1. The first patient was a 33-year-old housewife. She had had left sided pneumonia, with pleurisy, in 1927. In 1932 there was an episode of hemoptysis. No evidence of tuberculosis was found on clinical and roentgenographic examination. The patient remained in apparent good health until 1936 when she developed symptoms of a "chest cold." A chest film at this time revealed the presence of a 1 cm. density, productive in character, at the level of the second anterior rib on the left side. Just below this was a smaller productive nodule. She entered a sanatorium for three months.

Following her discharge another hemoptysis occurred and she came to the Cedarcrest Sanatorium, Hartford, Connecticut in August 1937. She was discharged two months later as non-tuberculous. She then remained asymptomatic except for intermittent small hemoptyses. When roentgen-rayed on March 29, 1940 at the Undercliff Sanatorium, Meriden, Connecticut, a uniform area of faint radiopacity was noted below the left clavicle, between the fifth and seventh ribs posteriorly, measuring about 3 cm. (figure 1). Infrequent small hemoptyses continued until May 1943, when the bleeding became profuse. After two days in a local hospital she transferred to the Undercliff Sanatorium on May 19, 1943.

Course in the sanatorium: With laminographic studies no definite cavity could be discovered within the infiltrative process involving the left upper lobe, although small areas of lesser density were seen in the 8 and 10 cm. planes. The left upper lobe bronchus was clearly visualized as running along the inferior border of the area of infiltration.

Laboratory findings: Red blood cells were 3,190,000, hemoglobin was 64 per cent, white blood cells numbered 9,900 with polymorphonuclears 76 per cent, eosinophiles 1 per cent, lymphocytes 13 per cent and monocytes 10 per cent. Urine specimens were negative. The patient expectorated little and the sputum was negative for tubercle bacilli both by culture and guinea pig inoculation.

A left pneumothorax was induced one month after admission to control hemoptyses. Following this, the patient had slightly blood streaked sputum without frank hemoptysis. The pneumothorax was not maintained and the left lung had fully reexpanded by roentgen-rays of October 12, 1943. The following day she began another series of hemoptyses. On October 19, a left phrenic crush was performed with the

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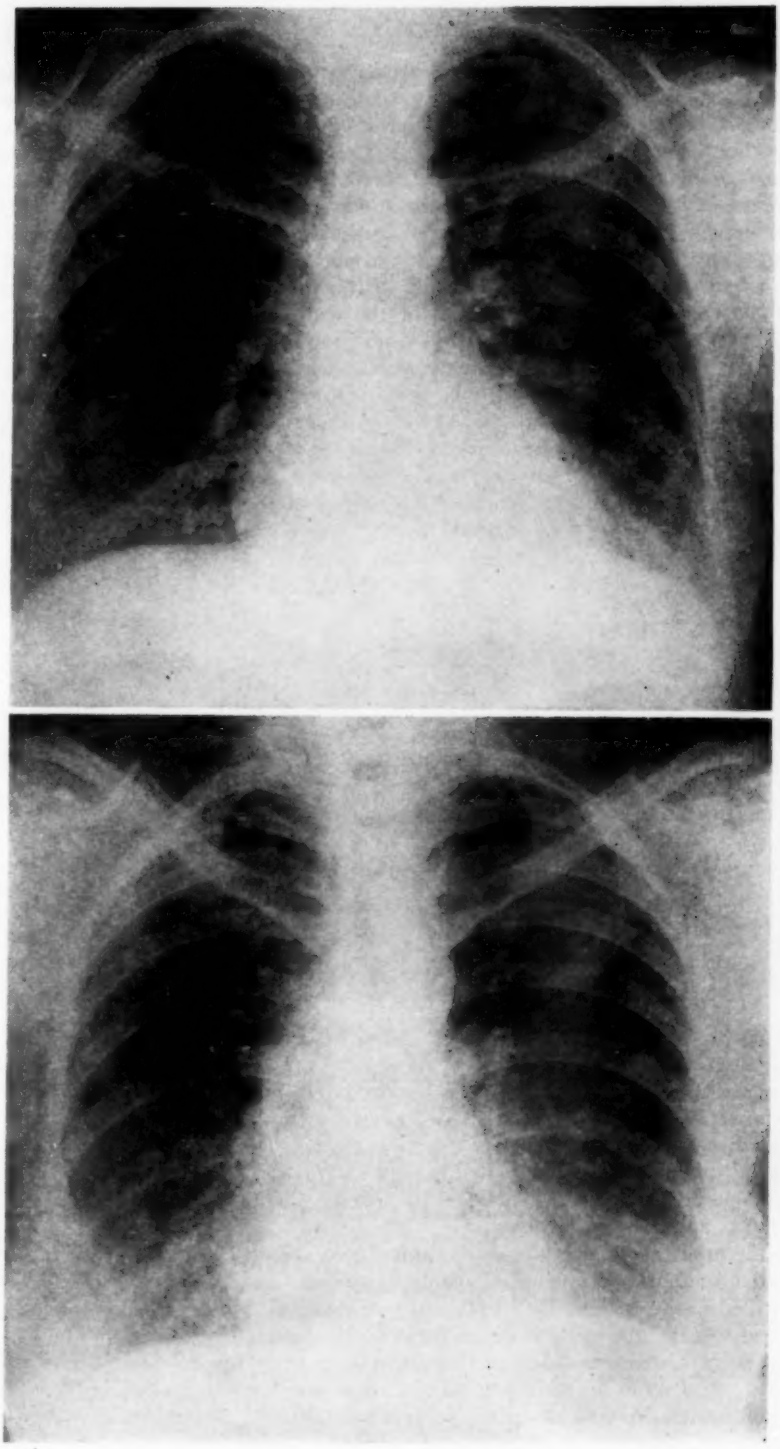

FIG. 1. (*above*) Case M. C., chest roentgenogram on March 29, 1940.
FIG. 2. (*below*) Case M. C., chest roentgenogram on October 19, 1943.

hope of controlling the hemoptyses, but satisfactory paralysis and rise of the diaphragm was not obtained. Chest roentgenograms at this time (figure 2) showed the lesion to be of the same size but denser than in June 1943. In addition a thin aerated crescent now overlay the superior surface of the lesion. During her stay at Undercliff, she was afebrile and asymptomatic except for a dull pain in the region of the left scapula at the time of her hemorrhages. The patient was transferred to the Uncas-on-Thames Sanatorium, Norwich, Connecticut on November 3, 1943 for surgical treatment. Laminography of the left apex showed a rounded, airless mass at the level of the second rib in the 8 and 9 cm. sections. Bronchoscopic examination was negative. No lesions were seen on examination of the oro- and nasopharynx and swabs implanted upon Sabouraud's medium yielded no growth.

In view of the history as well as of the roentgen-ray appearance and behavior of the lesion, it was thought that this was a tuberculous rather than neoplastic lesion. Because the patient was incapacitated by the recurrent hemoptyses, left upper lobectomy was performed on November 26, 1943. The postoperative course was not remarkable. A roentgenogram of January 14, 1944 showed the lower lobe about 60 per cent reëxpanded with evidence of thickening of the pleura on the left. She has been in good health at check-ups since then.

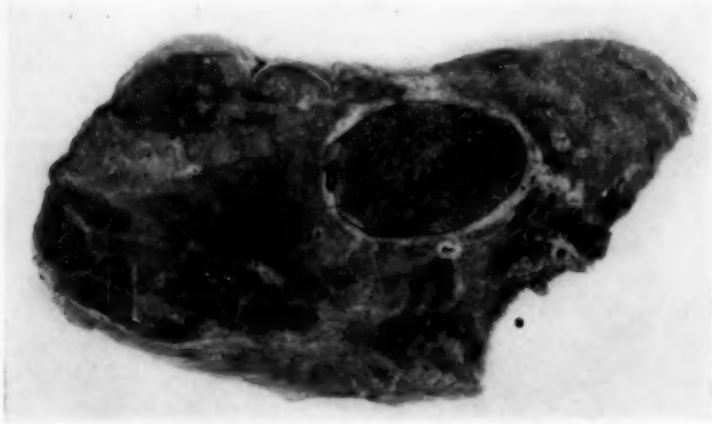

FIG. 3. Case M. C., left upper lobe.

Surgical pathology report: The removed left upper lobe was sectioned in the antero-posterior plane. An oval shaped cavity with a moderately thick fibrous tissue wall was discovered in the center of the parenchyma (figure 3). This cavity was filled by a dark brownish-purple laminated mass not unlike a blood clot. There was a small calcified nodule at the lower pole of the cavity. The remainder of the pulmonary parenchyma appeared uninvolved.

In the microscopic sections, the "cavity" was seen to be a cyst, lying at the end of a dilated bronchus. Bronchial elements (cartilage and smooth muscle fibers) could be identified in the cyst wall. In places there was well preserved columnar epithelium, while non-specific granulation tissue formed other parts of the wall. The contents of the cyst were a dense net of mycelia and spores of a fungus resembling aspergillus (figure 4).* In the surrounding parenchyma were several scattered foci of small round cell infiltration and of diffuse interstitial fibrosis. No tubercles were seen.

* Dr. Morris Tager of the Department of Bacteriology, Yale University was consulted on the mycological aspects of the cases reported. We are indebted for his advice.

Case 2. The second report concerns a 62-year-old white male. He had been a foreman in a machine shop for 37 years but for the last nine years had been a farmer.

In 1944 he entered a local hospital because of severe pain in the right chest. No roentgenograms were taken. White blood count was 10,200, with a normal differential count. Type eight pneumococci were found in the sputum and a diagnosis was then made of right lower lobe pneumonia. His temperature subsided with administration of sulfadiazine, but the drug was stopped on the fifth day when a rash appeared. After three days there was improvement in the skin lesions. He was discharged on the fifteenth day.

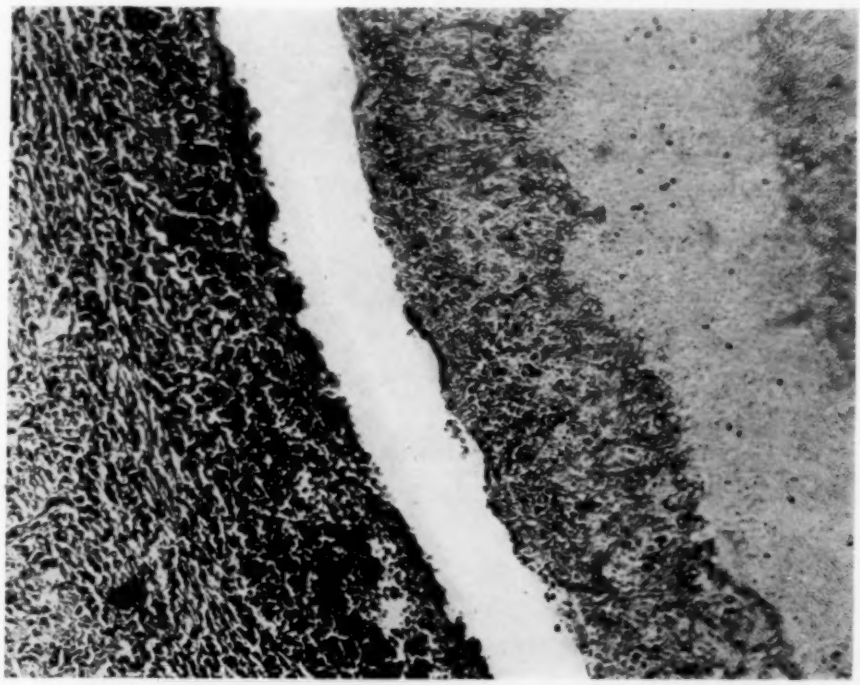

FIG. 4. Case M. C., microscopic section from cyst wall; H & E × 166.

After that time a macular eruption persisted over his body but he paid little attention to it. In August 1945, he expectorated about one dram of bright red blood. A chest roentgen-ray showed infiltration in both hilus areas and extending paravertebrally to the apices. There were also oblique linear densities at the level of the third to the fifth rib on the left as well as emphysema at both bases. He rested in bed for three weeks. Another roentgenogram, one month later, revealed an increase of the infiltration and also an effusion at the right base (figure 5).

The patient was admitted to the Uncas-on-Thames Sanatorium, Norwich, Connecticut on September 6, 1945. He was slightly dyspneic. A macular rash was present over the chest, abdomen and back.

Laboratory data: The red blood cells varied from 2,400,000 to 2,700,000, hemoglobin was 67 per cent, white blood count varied between 625 and 1,800. Differential count showed 32 to 52 per cent lymphocytes and 54 to 68 per cent polymorphonuclears. Serologic tests were negative for syphilis. The urine showed 1 + albumin and an occasional red blood cell but no casts. Since the patient did not expectorate, sputum was not available for examination. Agglutination tests for typhoid, paratyphoid and

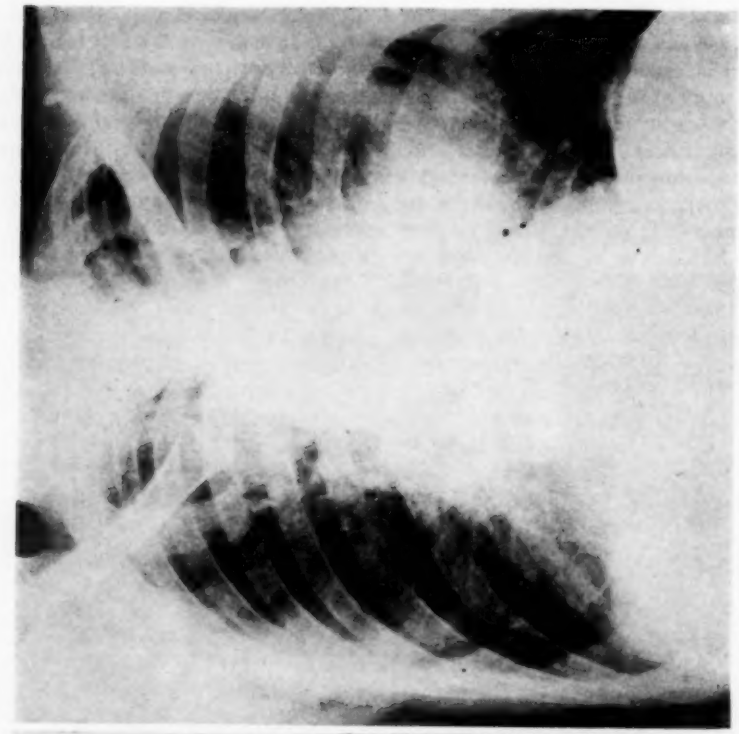

FIG. 6. Case A. C., chest roentgenogram on October 3, 1945.

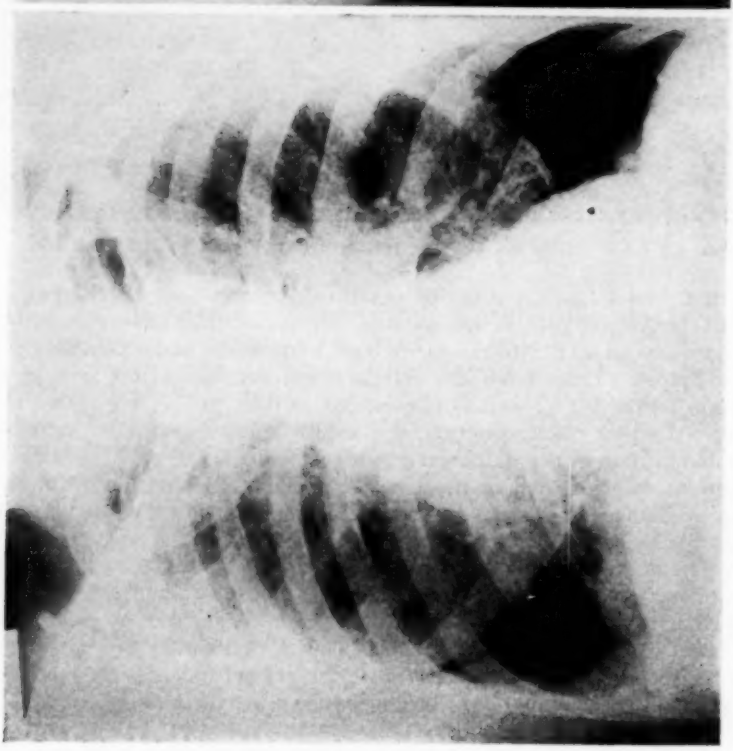

FIG. 5. Case A. C., chest roentgenogram on September 4, 1945.

undulant fever were negative. Blood cultures on the usual media did not yield any growth. Bone marrow obtained by sternal puncture showed aplasia. The patient received liver extract, Betalin complex, penicillin and transfusions.

On October 3, 1945 a roentgenogram (figure 6) showed almost complete clearing of the pleurisy but no other significant change on the right. On the left, however, a dense infiltration with a fuzzy border now radiated out from the hilus toward the base. Two adjacent rounded densities, one of them with a rarefied center, could be seen at the level of the fourth anterior interspace. The patient died on October 7, 1945. An autopsy was performed.

Gross pathology: Numerous reddish-purple, irregularly shaped maculo-papular lesions were seen over the trunk and extremities. These measured 2 to 15 mm. in diameter and slight hyperkeratosis was noted over some of them.

An extensive fibrinous exudate covered the epicardium.

The upper part of the right pleural space was obliterated by fibrous adhesions, while the lower part contained 300 c.c. of cloudy yellow fluid. Several round, well-

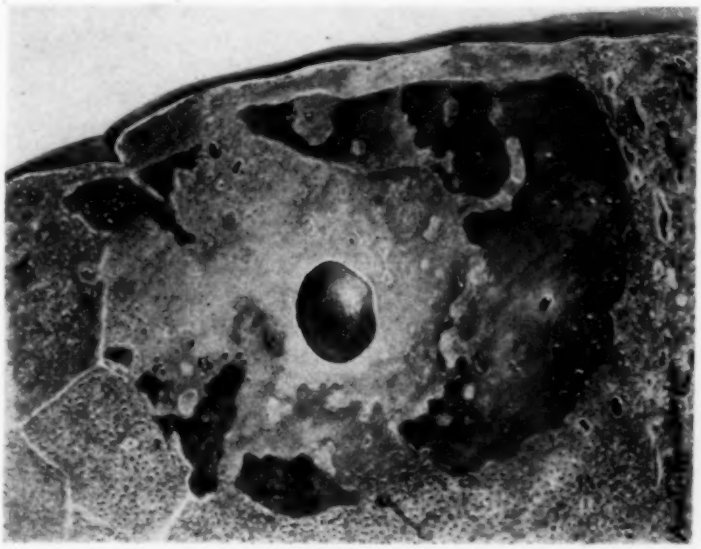

FIG. 7. Case A. C., left upper lobe.

defined, slightly raised, grayish-purple and moderately firm areas 8 mm. in diameter were found in the peripheral portions of the right upper and right middle lobe. The lateral segment of the right lower lobe was atelectatic.

The subapical segment of the left upper lobe was attached to the parietal pleura by numerous firm fibrous adhesions. The lung beneath them was bulging and consolidated. The cut surface of this lesion measured 9 cm. Peripherally, it showed a dark-purple cut surface with an occasional grayish pigmented remnant of interlobular septa (figure 7). Some of the alveoli adjacent to this lesion contained a hemorrhagic exudate. The central portion of the lesion was of grayish light-purple color and the outlines of bronchi and vessels were the only pulmonary structures that could be identified. A 1.5 cm. oval shaped cavity, lined by a grayish smooth wall and containing some hemorrhagic exudate, occupied the center of the consolidated area. A group of small abscesses was found in the lateral segment of the left lower lobe and a smaller similar group at the base. Thick pus-like yellow exudate filled their lumina.

Some of the intervening alveoli contained a dark red exudate while elsewhere slight fibrous connective tissue proliferation was noted. Mucopurulent material exuded from all bronchi. The hilar lymph nodes were enlarged. Their cut surfaces bulged and were of grayish purple hue.

The spleen was enlarged, of soft consistency and dark purple color. The Malpighian corpuscles could not be seen. The pancreas, adrenals, liver, gall-bladder and gastrointestinal tract were grossly negative. One enlarged lymph node was found in the mesentery. Its cut surface was yellowish-gray and fairly firm. Both kidneys showed numerous small abscesses containing yellow pus in the cortices and medullae. The pelves were lined by intact mucosa.

Other organs and structures were not remarkable.

Microscopic pathology: In sections from the periphery of the left upper lobe lesion, the alveolar walls were intact and the alveoli contained a fibrino-hemorrhagic exudate. Many of the vessels were occluded by antemortem thrombi with evidence in some instances of organization. Numerous mycelia and small spheroid bodies resembling spores were observed within these thrombi. While some of the mycelia had remained unstained others had absorbed a light-purple to dark-blue stain. Sections from the wall of the larger cavity and surrounding tissue revealed necrosis of the parenchyma with the alveolar shadows filled by an exudate of fibrin and cellular debris. Numerous mycelia, spores, and also fine mycelial filaments ending in a small solid head were seen in the parenchyma and within the lumen of the cavity as well as within the lumina of the vessels. With a Brown-Brenn stain the mycelia and spores appeared light yellow and the filaments gram positive. A van Gieson stain demonstrated splitting and fragmentation of the elastic lamina of the vessels. Mycelia piercing the wall of vessels (figure 8) and spores lying between the elastic lamina could be visualized. Occasional clumps of gram positive cocci were noted in both the preserved and the necrotic parenchyma.

Sections representing the groups of abscesses in the left lower lobe showed areas of caseous necrosis, cellular debris and surrounding hemorrhagic and necrotic alveoli. Numerous arborescent mycelia were seen throughout these lesions. Also present was an oval shaped structure composed of a dark purple center encircled by a concentric ring of pink and then of light purple staining material (figure 9). Under higher magnification, numerous fine radiating lines were seen and this was interpreted as a cross section through the head of a fungus mass.

Sections from other parts of the left and right lung revealed foci of hemorrhagic alveolar exudate. A few alveoli containing cellular debris were usually seen in the center of these lesions whereas at the periphery monocytic and plasma cell infiltration and an occasional multinucleated giant cell were noted. The muscle fibers of some of the smaller vessels were of pink wax-like appearance and showed loss of nuclei although the endothelium was intact. A perivascular exudate of round and plasma cells was seen. The bronchial walls also contained round and plasma cell infiltration. No microörganisms were discovered in the bronchial lumina.

Numerous small granulomatous lesions observed in the spleen and liver consisted of small spheroid bodies phagocytized by large mononuclear cells.

Sections of the skin revealed hyperkeratosis and vacuolization of some of the deeper epidermal cells. Small foci of plasma and monocytic infiltration as well as hemorrhages were present in the cutis. Monocytes containing two or three nuclei were seen. Some of the vessel lumina were filled by fine mycelial threads often ending in a small club-shaped head. These structures stained brown in the hematoxylin and eosin preparations.

Sections of the sternal bone marrow showed small infrequent groups of cells of the hematopoietic series, but for the most part complete aplasia of the bone marrow existed.

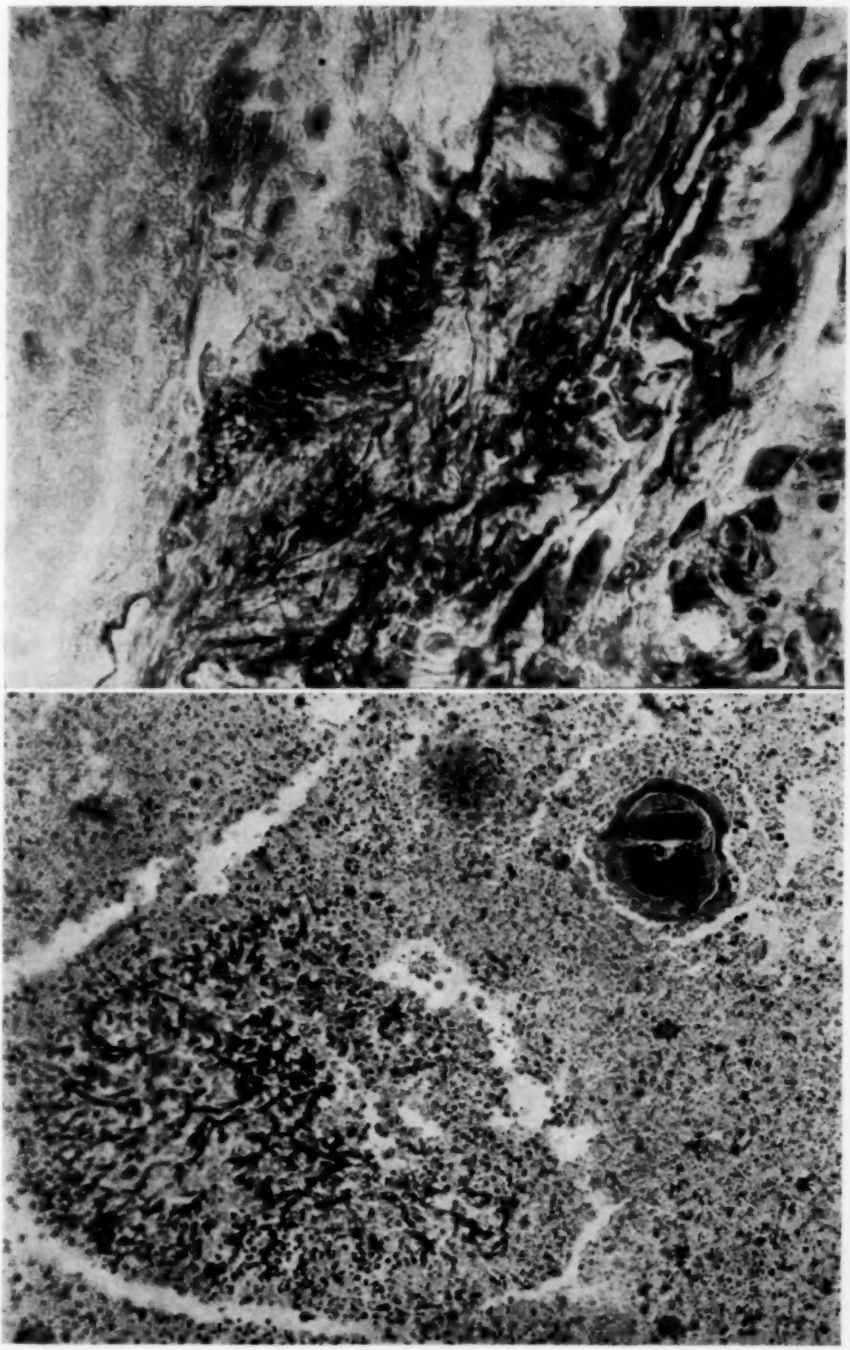

FIG. 8. (*above*) Case A. C., microscopic section from left upper lobe; Elastic-van Gieson stain × 360; note mycelium piercing wall of artery.

FIG. 9. (*below*) Case A. C., microscopic section from left lower lobe; H & E × 172; note mycelia and cross section through head of fungus.

Postmortem bacteriology: Tissue removed from the left upper lobe under sterile precautions was ground with saline and injected into a mouse, a guinea pig and a rabbit. In the mouse, which died four days later, abscesses were found in the mesentery and at the lower surface of the liver. No fungus was found in these lesions. The guinea pig was free of lesions after several weeks. The rabbit, sacrificed on the twenty-ninth day, showed an omental abscess from which aspergillus was recovered on culture. Part of the tissue removed at autopsy was implanted on Sabouraud-maltose media and growth of a fungus was obtained in three to four days. Growth at 37° C. was several times more luxuriant than at room temperature. The organism was identified by Dr. Kenneth Raper as *Aspergillus fumigatus Fresenius.**

Three rabbits were injected intravenously with light saline suspensions of the cultures from the Sabouraud's media. These animals showed labored respiration and paralysis of the hind legs three to four days after injection. In one of them, the white blood count dropped from 10,000 to 4,000 on the second day. The other two rabbits, however, showed no significant changes in their blood count or hemoglobin. Sections of the lungs of these animals revealed numerous small granulomatous lesions. Within some of them capillaries or precapillary vessels contained dark-staining mycelial threads. There was but little necrosis in the lungs. Numerous small foci of necrosis and polymorphonuclear infiltration were noted in the liver and kidneys but microorganisms could not be identified in them. Small myocardial infarcts were also found.

One rabbit was injected intravenously with a Seitz-filtrate of a culture suspension. No significant change in the white blood count occurred.

Discussion

The first of the two cases reported may be interpreted as a bronchiectatic cyst harboring a growth of aspergillus. It is remarkable that a fungus growing so well at body temperature showed so little pathogenicity. The mycotic infection did not invade the surrounding parenchyma or vessels and thus cure by surgical procedure was facilitated. The failure of the fungus to migrate into the surrounding tissue and the histology of the cavity wall lead to the assumption that the cavity was preformed and did not result from propagation of the fungus. The inflammatory reaction of the surrounding parenchyma indicates, however, that some interaction between fungus and host took place, and the febrile episodes of this patient may have been related to this.

The interpretation of the roentgenographic changes of the first case was difficult. The early films gave no clue to the existence of a cyst. The well defined oval-shaped lesion found on later examination (figures 1 and 2) suggested bronchial adenoma but the additional parenchymal changes and the small aerated crescent on the upper pole (figure 2) raised doubt as to this interpretation. Cavitation would be reconcilable with tuberculosis, but this diagnosis was undermined by the consistently negative sputum.

After the pathology of the lesion was studied a search of the literature disclosed a report of an almost identical case by Dévé.[4] This author assumed that the aspergillus infection was the primary factor and called the lesion megamycetoma. He pointed to the aerated zone at the upper pole of the lesion as a pathognomonic sign.

Although the pneumonia recorded in the history of the second case offers the possibility that it represented the first manifestation of the terminal disease,

* We wish to express our gratitude to Dr. Kenneth Raper, Northern Regional Research Laboratory, Peoria, Illinois.

the existence of a long standing skin exanthem diagnosed post mortem as mycotic raises the question whether skin or lung served as the primary focus of infection. The presence of lesions in other organs would classify this as a case of systemic aspergillosis.

The roentgen-ray changes of this case differ from what has been described as suggestive of fungus disease of the lung.[5, 6] They resemble the spread and metastases of cancer and were in fact interpreted as such by several roentgenologists. These lesions developed, however, over a period of less than two months and should support a diagnosis of mycosis.

The pathology underlying the roentgen-ray changes is that of a combination of interstitial and parenchymatous type of the disease [5] plus tissue necrosis hastened by the extensive occlusion of pulmonary vessels. The unrestricted penetration of all pulmonary structures in this second case is in striking contrast to the limited growth of the fungus in the first patient.

Leukopenia, and hypoplasia of the bone marrow have not, to our knowledge, been reported as complications of aspergillosis. It is unlikely that the sulfadiazine administered 18 months earlier would have such a protracted effect. The animal experiments, however, did not give full support to the assumption that this particular strain of aspergillus produces a substance toxic to the bone marrow.

The pulmonary lesions found in the experimental animals correspond to those reported by Lapham,[8] and the microörganisms were identified histologically. The lesions of liver and kidney were of an acute necrotizing character.

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ELECTROCARDIOGRAPHIC ALTERATIONS RESEMBLING THOSE PRODUCED BY MYOCARDIAL INFARCTION OBSERVED DURING A SPONTANEOUS ATTACK OF ANGINA PECTORIS *

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Occasionally opportunities have been afforded for securing electrocardiograms of patients with angina pectoris during a spontaneous paroxysm. These

* Received for publication June 18, 1946.
From the Department of Internal Medicine, Albany Medical College and the Albany Hospital, Albany, New York.

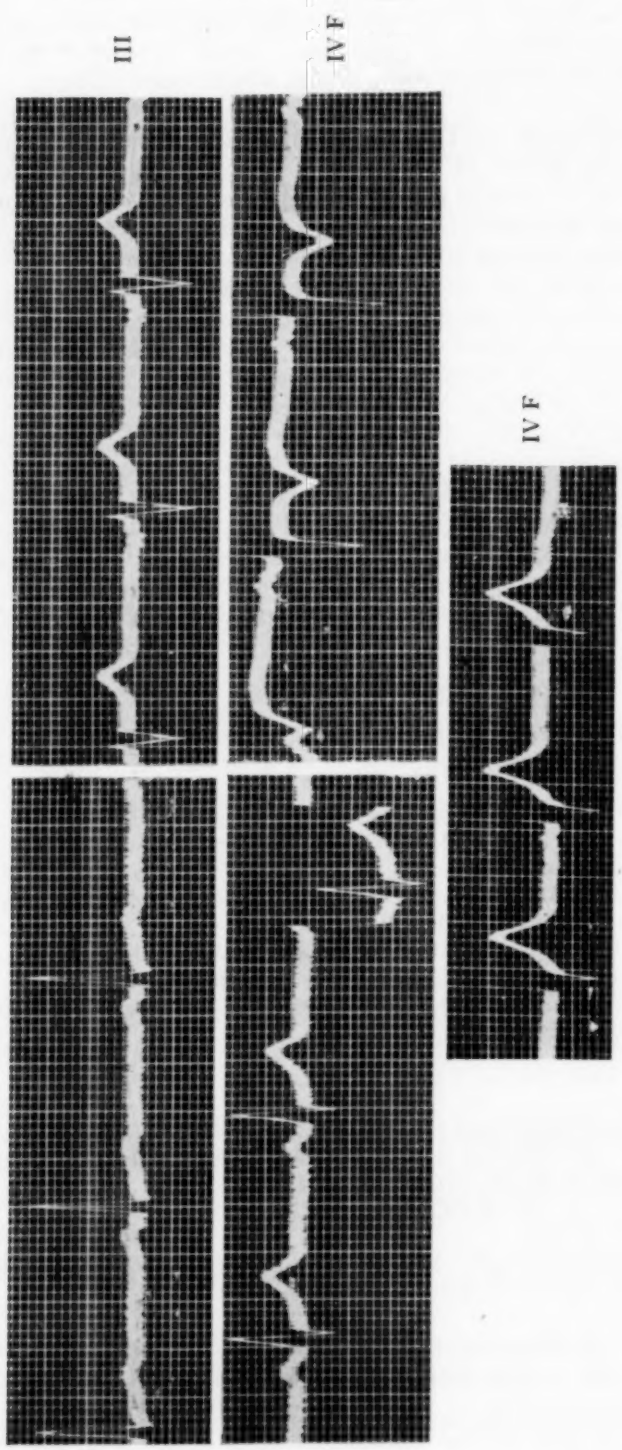

FIG. 1. *A*. Control electrocardiogram. Tracing taken when patient was free from pain, showing a low T-wave in Lead I and an inverted T-wave in Lead IV. *B*. Lead IV F taken immediately after relief of substernal distress by nitroglycerine (1/100 gr.). T-wave in Lead IV is now upright.

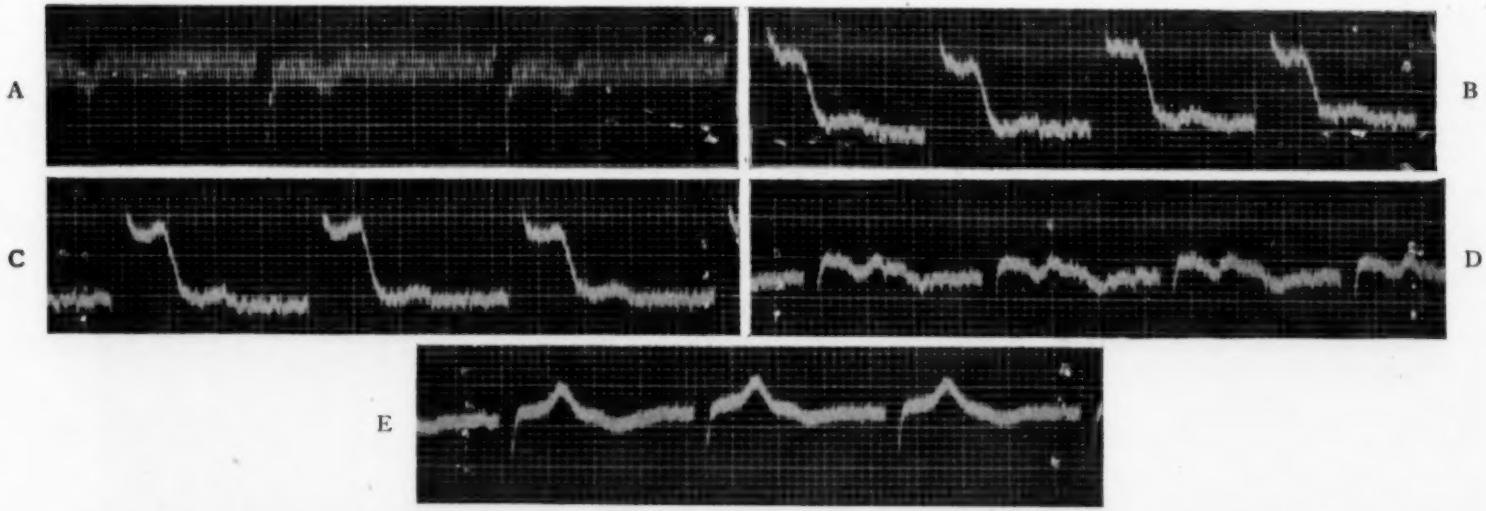

FIG. 2. All tracings in figure 2 are Lead IV F. *A*. Second record of patient at rest without pain. The T-wave is again inverted. *B*. About five minutes after *A;* patient had severe attack of substernal pain which occurred spontaneously. Striking elevation of the ST interval. *C*. One minute after patient received nitroglycerine (gr. 1/100) under tongue. No relief from pain and no change in ST segment. *D*. Thirty seconds after a second nitroglycerine tablet. Pain subsiding. Slight elevation of ST segment and partial inversion of T-wave. *E*. Two minutes after *D*. Pain completely relieved. Record now essentially normal and similar to figure 1B.

have shown distinct changes resembling those found after thrombosis of a large coronary artery.[1] We should like to place on record our electrocardiographic findings in a patient observed before, during, and after a spontaneous attack of angina pectoris.

Case Report

Mr. F. Van V., aged 46, was seen in the office by one of us (F. S. R.) on January 3, 1944, complaining of substernal distress on exertion. A brief history was obtained, an electrocardiogram was taken, and an appointment was made for a more complete examination three days later. This record showed left axis deviation, a low T-wave in Lead I and an inverted T-wave in Lead IV (figure 1A).

He returned three days later and a more detailed history was obtained. He stated that he had experienced severe substernal pain after doing heavy work, hurrying up stairs, etc. for the preceding four months. The pain had been so severe that he had been forced to stop and rest, whereupon the distress would gradually subside. For the past three weeks he had had similar attacks of pain at rest. On several occasions he was awakened from his sleep with severe angina. Excitement or nervous tension often precipitated attacks.

Physical examination was essentially negative. Blood pressure was 120 mm. Hg systolic and 80 mm. diastolic. Blood Wassermann test was negative. Urinalysis was negative. During the examination, he had an attack of substernal pain. It was apparently severe, and the heart suddenly became rapid and irregular (coupled rhythm). Fearing serious developments the patient was given one 1/100 grain nitroglycerine tablet under his tongue. Within a minute the pain began to subside and the cardiac irregularity disappeared. A fourth lead electrocardiogram was taken within five minutes after the pain subsided (figure 1B).

The patient was again seen in the office eight days later. He had had attacks nearly every day, several without exertion. All had been promptly relieved by nitroglycerine. Because of the marked change of the T-wave in Lead IV noted on the previous visit, Lead IV F was repeated before the patient was interviewed or examined. Unfortunately the record was disturbed by alternating current due to a faulty ground connection, but the general form was the same as in the original record, the T-wave being inverted (figure 2A).

During the examination about five minutes later he complained of severe chest pain. He was immediately returned to the electrocardiograph room and Lead IV F was again taken, showing the striking change seen in figure 2B. A 1/100 grain nitroglycerine tablet was dissolved under the patient's tongue. After one minute he obtained no appreciable relief, and another record was taken showing very little change (figure 2C). A second tablet of nitroglycerine was given and within 30 seconds the patient showed and expressed marked relief. Another record taken shows striking change in the level of the ST segment (figure 2D). After a two minute interval the pain had entirely gone, and a final record at this time showed return of the T-wave to the upright form (figure 2E).

On January 28 the patient was again seen in the office, and had another attack of severe chest pain. This time the three standard leads of the electrocardiogram were taken during the attack, and after relief was obtained by nitroglycerine. Figure 3A is the record taken during the attack and figure 3B two minutes later when the pain had completely subsided. While there are definite changes in the T-waves in Leads I and III, these are much less striking than those previously observed in Lead IV. No disturbance in rhythm was ever detected except during the first attack on January 6.

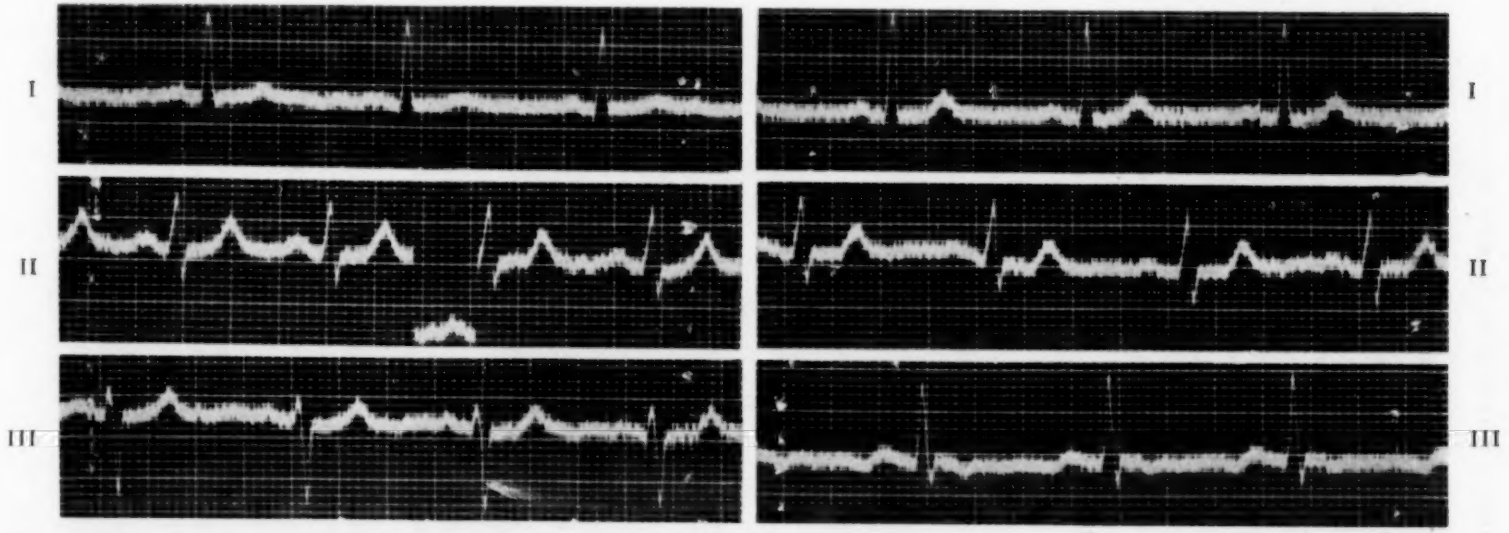

FIG. 3. Three standard leads. *A*. During another severe spontaneous attack of angina. T_1 low and T_3 upright. *B*. Two minutes after complete relief of pain from nitroglycerine (gr. 1/100). T_1 higher and T_3 mainly inverted.

Comment

The electrocardiographic changes recorded in this patient during an attack of angina pectoris are similar to those observed after occlusion of a large coronary artery, and indicate a profound disturbance in the coronary circulation. These findings would support the opinion that anginal attacks are caused by myocardial ischemia. Opinions have differed regarding the pathogenesis of the myocardial ischemia. Some believe it to be due to an increase in the work of the heart, while others believe that it is brought about by an alteration in the caliber of the affected coronary artery (coronary spasm). Our observations would support the latter theory, inasmuch as the profound electrocardiographic changes appeared and disappeared while the patient was at rest and with no significant increase in the heart rate.

Summary

Electrocardiographic changes resembling those observed after a myocardial infarction are presented from a patient during a spontaneous attack of angina pectoris.

A diminution in the caliber of the affected coronary artery rather than an increase in the work of the heart is suggested as the probable pathogenesis of the myocardial ischemia.

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BARBITURATE POISONING: COMBINED USE OF RESPIRATOR, FLUID, CENTRAL NERVOUS SYSTEM STIMULANTS AND PRESSOR AGENTS *

By David T. Dresdale, M.D., Hurley L. Motley, M.D., John R. West, M.D., and James K. Alexander, M.D., *New York, N. Y.*

This case is presented to demonstrate the use of a respirator, combined with parenteral fluids, central nervous system stimulants and pressor agents, in sustaining life for three days in a patient deeply comatose from barbiturate poisoning.

The patient was a 63 year old hypertensive and diabetic white woman, with suicidal tendencies, who had taken, as well as could be determined, approximately 2 gm. of Sodium Seconal and 0.6 gm. of Sodium Amytal, eight to ten hours before admission

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to the emergency ward at Bellevue Hospital. At the time of admission the patient was deeply cyanotic, unresponsive to stimuli, a-reflexic and almost pulseless. The blood pressure was unobtainable. Respiratory movements consisted of a shallow gasp occurring every one to two minutes. She was described as having been in the above condition for at least one hour before being brought to the hospital. After an intravenous injection of epinephrine hydrochloride (0.5 mg.) was given, the blood pressure became obtainable and the pulse palpable. Oxygen (100 per cent) at the rate of 10 liters per minute was administered by means of an OEM (Oxygen Equipment Mask) and artificial respiration was started at once employing the "squeeze the chest" method. Although the blood pressure could be maintained erratically by intravenous epinephrine every three to four minutes, she remained apneic and deeply cyanotic. This method of artificial respiration has been found to ventilate the lungs on an average less than one liter per minute in similar subjects.[1]

In view of the inadequate ventilation, the Pneumatic Balance Respirator, "Burns Model," hereafter referred to as the PBR, was applied.

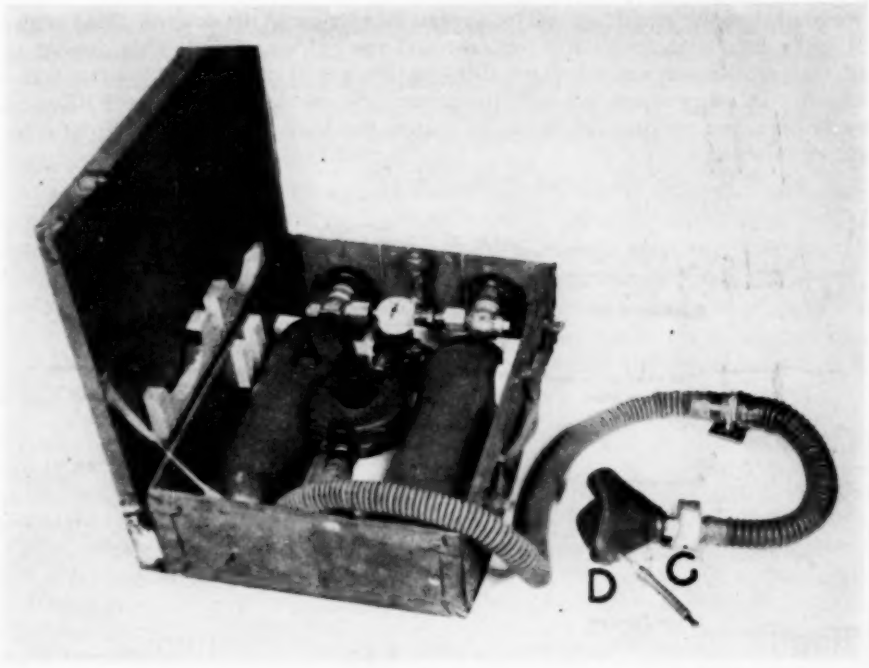

FIG. 1. The PBR Respirator Unit. (A) High pressure oxygen cylinder. (B) Pressure demand regulator. (C) PBR (Pneumatic Balance Respirator, "Burns Model"). (D) Mask.

The PBR is a small and compact device (figure 1), developed by the Army Air Force,[1, 2] for giving artificial respiration by converting continuous positive pressure into intermittent positive pressure.

The entire artificial respiration apparatus consists of (*a*) a high pressure oxygen tank; (*b*) a pressure demand regulator, of the type used by the Army Air Force, which supplies oxygen on inspiratory "demand" from the tank, and in addition a continuous pressure ("line pressure"), which may be varied by

adjustment of the regulator, from 12 cm. of water up to 30 cm. of water; (*c*) the PBR; (*d*) anesthesia mask, or in deep coma cases such as this one, an intratracheal tube; (*e*) connecting tubing.

The operation of the Pneumatic Balance Respirator (PBR) is such that it allows the compressed gas to pass from the pressure demand regulator to the patient (positive pressure inspiration), until the inspiratory pressure reaches about 75 per cent of the "line pressure," at which point the inspiratory valve of the PBR closes and expiration then takes place passively, expired air passing out through small ports in the side of the PBR. As expiration is completed, the inspiratory valve re-opens and the compressed gas flows again from the high pressure cylinder through the regulator and the PBR to the patient.

A clearing of the cyanosis was noted almost immediately after the PBR was applied, using an endotracheal tube and a line pressure of 16 cm. water with 100 per cent oxygen. One half hour later spontaneous respiratory movements were restored, but the PBR was continued because respirations were shallow and cyanosis returned upon removal of the respirator. The oxygen saturation of the arterial blood with the PBR seven hours later was 102 per cent and the pH was 7.37. This finding gave proof that ventilation was adequate although the actual ventilatory volume was not measured. In other apneic subjects the pulmonary ventilation with the PBR cycling properly on a line pressure of 16 cm. of water, has been found to vary from 6 to 10 liters per minute.[1]

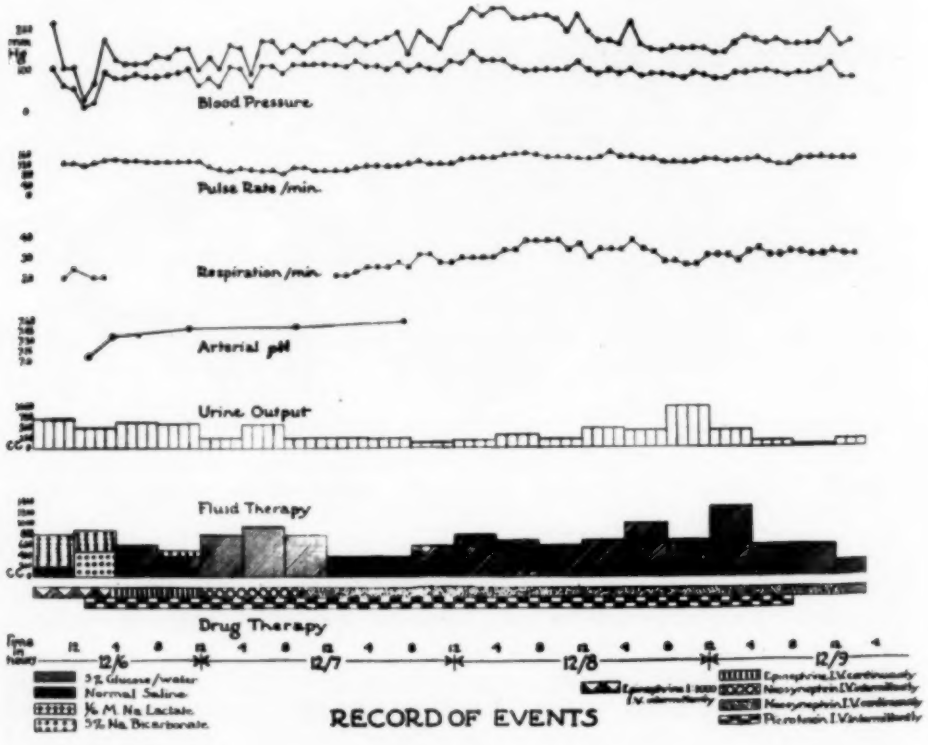

FIG. 2.

After an initial period of about one and a half hours on the PBR, the respirator was removed so that the stomach could be washed out. Bubbling râles were heard in both lungs after the gastric lavage; it was suspected that some fluid may have been aspirated. These râles cleared shortly after the PBR was reapplied and the lungs remained relatively clear of moisture during the remainder of the time (76 hours) that the respirator was used. The clearing of moisture in lungs with the PBR has been observed in other coma cases.[1, 3]

The arterial blood pressure was maintained throughout the 78 hours by means of the sympathomimetic drugs, epinephrine and neosynephrine. During the first eight hours epinephrine in 0.5 mg. doses was given intravenously at intervals with wide fluctuation of the blood pressure and rapid pulse rate. During the next eight hours the blood pressure was maintained at a more or less constant level (average 130/80) by regulating the inflow of infusion fluids containing epinephrine, 8 mg. per liter. However, the tachycardia persisted.

Neosynephrin was substituted for epinephrine 16 hours after admission. A total of 900 mg. of neosynephrin was given during the next 62 hours (figure 2). It was given at first in doses of 0.3 mg. intravenously, intermittently, and the blood pressure was sustained with a slower heart rate. Neosynephrin was then added to the infusion fluid, 100 to 200 mg. per liter, and by controlling the rate of flow of the infusions the blood pressure was maintained for the following 52 hours at the desired level (average 160/90 mm. Hg) with a much slower pulse rate than with the epinephrine (figure 3). An exception to this was noted for a period of time when picrotoxin seemed to have its maximum effect.

Keys and Violante,[4] in man, and Landis and Geiter,[5] in dogs, have shown that neosynephrin will elevate and maintain blood pressure without an undesirable accompanying tachycardia. Because of this property neosynephrin has been described as the pressor drug of choice in surgical shock [6] and anesthesia.[7, 8] Since the case described here, we have had the opportunity to observe the use of neosynephrin administered intravenously with infusion in six coma cases with complete apnea and vasomotor collapse. In each case the blood pressure was restored and maintained with a normal pulse rate.

It might be noted that injections of caffeine sodium benzoate in doses of 0.5 gm., intravenously, or benzedrine sulfate in doses of 10 mg., intravenously, concomitant with the epinephrine did not appear to have any appreciable effects and were discontinued early.

In an effort to stimulate the central nervous system, repeated doses of picrotoxin totalling 940 mg. were given intravenously over a 67 hour period. The doses varied from 10 mg. every 20 to 40 minutes during the first day to 20 mg. every 30 to 60 minutes during the next two days. Shortly after picrotoxin was started the time interval between injections of epinephrine necessary to maintain the blood pressure was considerably lengthened, the respiratory rate was increased, the corneal reflex (used as a guide for the administration of picrotoxin) became active and was maintained for the greater part of the time, and the patient gagged several times on the intubation tube. The deep tendon reflexes never became active.

The patient was in severe acidosis at the time of admission. A blood arterial pH taken several hours after starting the PBR and after 960 c.c. of 1/6 M. Na lactate had been given intravenously was 7.09. Three hours later and after 500 c.c. of 5 per cent Na bicarbonate had been given intravenously the arterial pH was 7.37. Thereafter the pH was kept within normal limits or slightly on the alkaline side. This was accomplished by the combined use of alkaline, normal saline and glucose and water infusions, adequate pulmonary ventilation with sufficient removal of the CO_2 and the

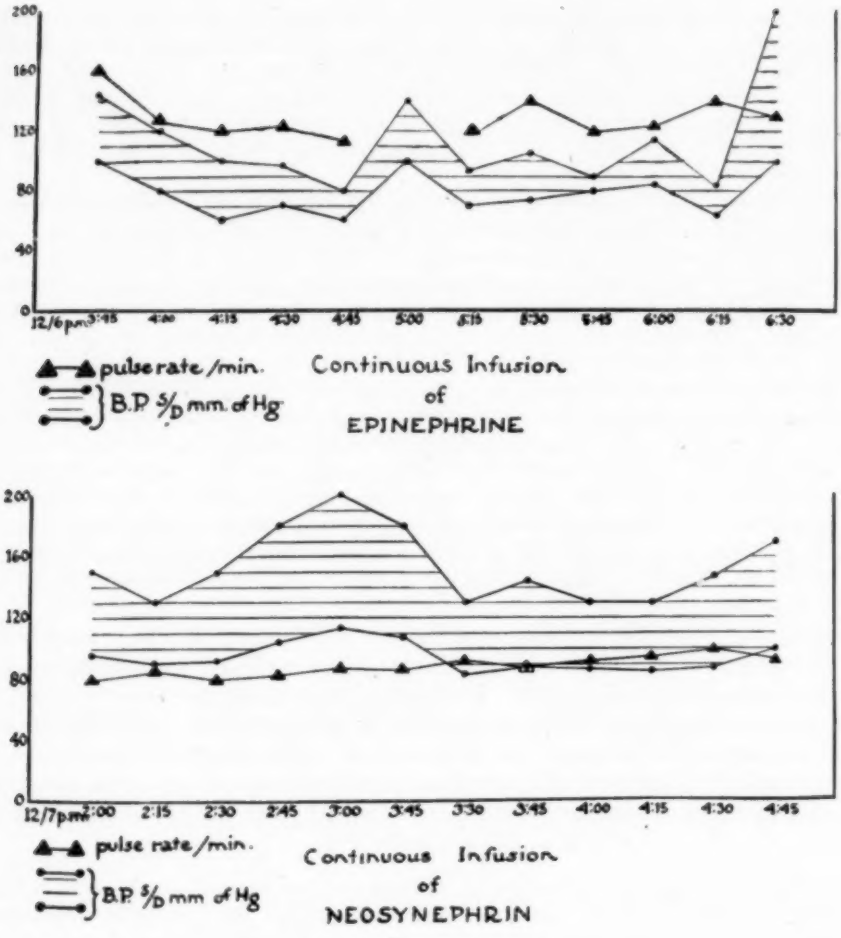

FIG. 3.

maintenance of good renal function. The latter was probably related to an adequate mean arterial pressure maintained throughout most of the 78 hours.

A total of 13,510 c.c. of fluids, containing 11 gm. of Na, was administered over the 78 hour period and during this time 7480 c.c. of urine were excreted (figure 2). The hematocrit taken on the second day was normal (49 per cent). All glucose given was covered by insulin.

The patient never recovered consciousness, having apparently suffered irreversible central nervous system changes. This was probably brought about by the prolonged period of anoxia and extreme acidosis prior to treatment. At the end of 78 hours the respirator was removed and the patient was tested breathing air spontaneously. For eight minutes she continued regular shallow respirations with no cyanosis, then suddenly stopped breathing. An autopsy was not performed. The patient was signed out by the medical examiner as barbiturate poisoning on the basis of clinical findings and urine and gastric contents positive for barbiturates.

In concluding, we believe this case illustrates how the combined and judicious use of a respirator, alkalis, fluids, central nervous system stimulant and pressor

drugs can cope with the manifold problems presented by an unconscious subject with the possibility of maintaining life for long periods, thus favoring a better chance of a successful recovery.*

The authors desire to express their appreciation for the helpful suggestions and advice given by Dr. Dickinson W. Richards, Jr., Director of First Medical Division, Bellevue Hospital, and for the coöperation of the members of the First Medical Division house staff.

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* More recently, a similar type of patient with barbiturate poisoning who was deeply comatose, apneic, cyanotic, and pulseless on admission, was treated in a similar manner. The PBR was removed after 24 hours at which time spontaneous respirations were adequate for maintaining normal respiratory gas exchange. This patient regained consciousness two days after admission and made an uneventful recovery.

EDITORIAL

BCG VACCINE

THE factors which determine immunity from tuberculosis differ substantially from those which are operative in the case of many other infections. Humoral antibodies appear to play at most a minor rôle, and resistance depends primarily upon an altered reactivity of the tissue cells. Although some degree of immunity may be produced in animal experiments by the inoculation of killed organisms, any notable degree of protection depends upon the presence of living tubercle bacilli in the body. All practicable methods of immunization are based upon the observation—which has been confirmed by innumerable experiments—that inoculation of animals with a strain of tubercle bacilli of low virulence may delay or prevent the development of a progressive generalized infection if the animal is subsequently inoculated with a virulent strain. Such an immunizing infection is regularly accompanied by a hypersensitiveness to tuberculin, and a tuberculin test is the most practicable way of determining its presence. It is probable, however, that hypersensitiveness to tuberculin is not an essential and perhaps not even a useful manifestation of the immunity reaction.

Although the incidence of tuberculosis has been substantially reduced by the measures currently employed, it is still all too prevalent and continues to be a major health problem. A safe and reasonably effective method of increasing resistance by vaccination would be an important supplement to these measures. It would be particularly valuable in the case of infants and also of young adults such as nurses and medical students who are unusually exposed to infection because of an unfavorable environment or occupational hazards. To be useful, however, vaccination must be carried out before infection is naturally acquired—while the tuberculin reaction is still negative—and it must antedate infection by a sufficient interval to permit the development of immunity, preferably at least one month. There is no evidence that vaccination alters the course of an established infection. The rationale of the procedure is sound. It should be safer for the individual deliberately to establish a primary infection with a strain of low virulence than to await almost inevitable infection under natural conditions with a strain of unpredictable but certainly of higher virulence.

BCG (bacillus of Calmette and Guérin) is a bovine strain of tubercle bacillus which was isolated in 1906 from the milk of a tuberculous cow. This was cultivated in Calmette's laboratory in the Pasteur Institute in Paris on media which were regarded as unfavorable for the maintenance of virulence. After 13 years' cultivation its virulence had become so attenuated that it caused only localized nodular lesions in guinea-pigs and did not give rise to a generalized infection. It still produced tuberculin in cultures, however, and animals which had been inoculated with it showed a significant degree of

protection against subsequent injections of virulent strains of tubercle bacilli.

On the basis of these observations Weil-Hallé and Turpin (1921) began the immunization of infants, at first administering the vaccine by mouth. As this resulted in only a small proportion of "takes" as indicated by the development of a positive tuberculin reaction, they changed (1924) to subcutaneous injections. After the safety of the procedure appeared to be established, it was used on an increasing scale in continental Europe where, it has been estimated, the vaccine has been administered to over 5,000,000 individuals. It has also been used fairly extensively in South America. In the United States, however, it has been used only to a very limited extent because of skepticism both as to its safety and its effectiveness.

Vaccination fell into temporary disrepute in Europe following the death in Luebeck, Germany, in 1930 of 77 vaccinated infants from progressive tuberculosis. Later, however, this was proved to be the result of a laboratory error in which a virulent strain of tubercle bacilli was substituted for BCG. In this country, doubt as to its safety has been based rather on the theoretical possibility that the culture might still contain some virulent organisms or that it might unexpectedly regain some measure of its original virulence while under cultivation. This view received some support from a report of Petroff et al.[1] that they had succeeded in dissociating their BCG culture into rough and smooth colonies and that strains derived from the latter at times were capable of producing progressive disease in animals. Many more recent attempts to confirm these observations with other strains of BCG have uniformly failed. No one has been able to prove that progressive disease in human beings has ever followed the use of the vaccine, and its safety in this respect is now generally acknowledged.[2]

Subcutaneous injections of BCG were often followed by troublesome local reactions consisting of necrosis and ulceration which might take several weeks to heal. Necrosis and sloughing of the regional lymph nodes were also frequent and often left unsightly scars. This difficulty was reduced by the substitution of intracutaneous for subcutaneous injections by Wallgren,[3] and it has been practically eliminated by the multiple puncture method of Rosenthal.[4] A few drops of a culture suspension of suitable density are placed on the sterilized skin of the arm, and with a sharp needle multiple skin punctures are made through the vaccine just as is customarily done in vaccination against smallpox except that the punctures are made somewhat more deeply and are more widely spaced. This results in the development of a small nodule at the site of each puncture which may attain a diameter of 3 to 6 mm.

[1] Petroff, S. A., Branch, A., and Steenken, W., Jr.: Study of Bacillus-Calmette-Guerin (BCG): Biological characteristics, cultural "dissociation" and animal experimentation, Am. Rev. Tuberc., 1929, xix, 9–46.

[2] Report of a conference on BCG vaccination, Pub. Health Rep., 1947, lxii, 346–350.

[3] Wallgren, A.: Intradermal vaccinations with BCG virus: preliminary note, Jr. Am. Med. Assoc., 1928, xci, 1876–1881.

[4] Rosenthal, S. R.: The multiple puncture method of BCG vaccination, Am. Rev. Tuberc., 1939, xxxix, 128–134.

and which subsides after about a month without causing discomfort, necrosis at the site of the vaccination or in the regional lymph nodes, or appreciable scarring. The effectiveness of the vaccination in inducing a mild infection is indicated by the development of a positive tuberculin reaction in over 99 per cent of the cases.[5]

The practicability of the procedure has been confirmed by many other investigators, among these Birkhaug.[6] He carried out a careful study in guinea-pigs and showed that if an adequate number of punctures (30 to 60) were made, the animals developed a substantial degree of resistance to subsequent infection with a virulent culture. This was at least equal to if not greater than that induced by scarification or intracutaneous injection. He subsequently used the method in vaccinating over 3000 human beings with no untoward results except minute local abscesses in 3.8 per cent of the subjects, which were not troublesome and which healed promptly. Of 1500 subjects so vaccinated, 98 per cent gave a positive tuberculin reaction two months later.

In spite of the large number of individuals who have been vaccinated and the long period of observation since vaccination was begun, it is far more difficult to reach any valid conclusion as to its effectiveness in reducing the morbidity and mortality from tuberculosis. Rosenthal[5] has collected and summarized many of the reported studies, chiefly from European countries. These appear to show a reduction in mortality among the vaccinated to a figure from one-third to one-fifth of that in the controls. In brief, however, these figures are not convincing because in few if any of the series do the "controls" constitute a group which is strictly parallel and comparable with the vaccinated.

The need for adequately controlled studies has been fully appreciated in this country, and a few have now progressed to a point which permits some conclusions to be drawn. Several studies have been made among nursing personnel and medical students. Although these are limited in the numbers studied and not so strictly controlled as is necessary for a crucial test, they are in harmony in showing a reduction of infection among the vaccinated. Thus Ferguson[7] reported that 0.825 per cent of 1005 nurses, vaccinated intracutaneously, in eight Saskatchewan general hospitals developed manifest tuberculosis during a period of 2.5 years, as compared with 3.82 per cent among 759 nonvaccinated individuals with originally negative tuberculin reactions. In three tuberculosis sanatoria the corresponding figures during a period of observation of about a year were 2.46 per cent for the 203 vaccinated and 15.9 per cent in 113 nonvaccinated individuals. The lesions in

[5] ROSENTHAL, S. R., BLAHD, M., and LESLIE, E. I.: Ten years' experience with BCG (experimental and clinical), Jr. Pediat., 1945, xxvi, 470–480.

[6] BIRKHAUG, K.: Protective value of the intracutaneous and percutaneous methods of BCG vaccination (comparative experimental investigation), Acta med. Scandinav., 1944, cxvii, 274–312.

[7] FERGUSON, R. G.: BCG vaccination in hospitals and sanatoria of Saskatchewan, Canad. Jr. Pub. Health, 1946, xxxvii, 435–451.

those who developed the disease were less extensive in the vaccinated group. Rosenthal [8] has reported similar results.

Of the studies in North America carried out on the general population, three will be summarized. Baudouin [9] has reported a study based on the vaccination of over 20,000 infants in Canada and observed over a period of 11 years. Restricting his report to children who were exposed to open cases of tuberculosis in their homes, he found that the mortality from tuberculosis in 793 vaccinated cases was about 70 per cent less and the morbidity 47 per cent less than in 1239 controls so exposed. In his series the resistance seemed to be maintained throughout the period of observation of seven years.

Aronson et al.[10] reported an extensive study carried out on Indians from one to 20 years of age, living on four reservations in the United States and in 12 communities in Alaska. The economic level of the group was low, and there was a high degree of exposure to tuberculosis. There were 1550 (intracutaneously) vaccinated individuals and a satisfactory control group of 1457 with negative tuberculin reactions who were not vaccinated. These were followed for six years or more, by means of repeated physical examinations, roentgenograms and tuberculin tests. The mortality was 4 among the vaccinated, all starting during the first two years, as compared with 28 among the controls, which were fairly evenly distributed over the six year period. The number showing manifest disease was 40 among the vaccinated, 4.7 per 1000 person-years, and 185, or 24.3 per 1000 person-years, in the controls. The latter were evenly distributed over the six year period, but the rate among the vaccinated fell progressively from 11.8 during the first year to less than 1 per 1000 person-years during the sixth year. This suggested that the degree of protection increased rather than decreased during this period under the conditions obtaining in this group.

The most extensive carefully controlled study is that of Rosenthal et al. carried out in newborn infants in Chicago, among a low income group in which there was a relatively high degree of exposure to tuberculosis. The infants were largely those delivered at the Cook County Hospital. The families were examined, and if there was a case of demonstrable tuberculosis in another member of the household, the infant was isolated for from six to 12 weeks before being returned to the home. Infants in the control series, subject to such exposure, were similarly isolated. The results of the first seven years' observation were reported in 1945,[5] and a later report covering the same group has recently been published.[11] Of the children not directly

[8] ROSENTHAL, S. R.: The use of BCG vaccination among medical and nursing students, Hospitals, 1943, xvii, April, 75–78.

[9] BAUDOUIN, J. A.: Vaccination against tuberculosis with BCG vaccine, Canad. Jr. Pub. Health, 1940, xxxi, 362–366.

[10] ARONSON, J. D., and PALMER, C. E.: Experience with BCG vaccine in the control of tuberculosis among North American Indians, Pub. Health Rep., 1946, lxi, 802–820.

[11] ROSENTHAL, S. R., LESLIE, E. I., and LOEWINSOHN, E.: BCG vaccination in all age groups. Methods and results of a strictly controlled study, Jr. Am. Med. Assoc., 1948, cxxxvi, 73–79.

exposed to tuberculosis in the household, among 1417 vaccinated by the multiple puncture method there were 11 cases of demonstrable tuberculosis as compared with 39 cases among 1414 controls, giving morbidity rates per 1000 person-years of 1.95 and 6.46 respectively. There was one death from tuberculosis in the vaccinated and seven in the control group. Of the children directly exposed to tuberculosis in the household there were two cases of tuberculosis (with no deaths) in 151 vaccinated children, whereas in the control group of 105 there were five cases with four deaths, giving morbidity rates of 3.86 and 17.60 per 1000 person-years. As the control groups in this study were adequate, the figures must be regarded as significant.

The interest aroused by these observations resulted in a conference of those actively engaged in this work, which was held Sept. 7, 1946, under the auspices of the United States Public Health Service.[2] It was recommended that BCG vaccine not be made available commercially at present but that extensive investigations be carried out coöperatively with recognized research groups, especially in population groups highly exposed to tuberculous infection. The Tice Laboratory in Chicago has been designated as a central laboratory for preparation of the vaccine for such studies.

To determine with any precision how much protection is afforded, how long it lasts, and what plan of vaccination will best produce and maintain this will require a great deal more work and protracted observation, probably for at least two decades. For the present, one may conclude that BCG vaccine is safe and that it need not cause troublesome local reactions if properly administered. It also appears to give a significant degree of protection throughout the relatively limited periods (about six years) during which the vaccinated groups have been observed. It seems possible that this may be prolonged or restored by revaccination if the tuberculin reaction becomes negative, as has been Rosenthal's practice in his group.

As with any type of vaccination, the immunity produced by BCG is only relative, and if the degree of exposure (size of the inoculum) is great enough or probably if the virulence of the infecting strain is sufficiently high, the immunity may be overcome and progressive disease develop. In heavily exposed groups, at least, BCG promises to be a valuable addition to the preventive measures now generally employed but not a substitute for them. If these preliminary conclusions are confirmed by the work now in progress, we may hope that the vaccine will soon be available for use on a more extensive scale.

P. W. C.

REVIEWS

The Chemical Kinetics of the Bacterial Cell. By C. N. HINSHELWOOD, F.R.S. × + 284 pages; 16 × 24.5 cm. Oxford University Press, New York. 1947. Price, $6.75.

The writer has posed in this volume the interesting problem of the principles of applicability of chemistry and physics to the living bacterial cell. Using the Langmuir isotherm and other physicochemical relationships, the writer applies these to the metabolism of the living bacterial cell.

Of special interest to the physician is the problem of adaptation of bacteria to drugs. Upon this phenomenon the development of drug fastness probably depends. The writer also develops in a mathematical manner the phenomenon of lag concentration graphs, of bacteria in normal media and in the presence of familiar anti-infective drugs.

The problem of bacterial variants is discussed from a physicochemical standpoint with regard to their environment and the action of drugs.

The death rate of bacteria is discussed from a mathematical viewpoint. The author closes the book with an excellent discussion of the second law of thermodynamics in relation to living cells, and challenges the reader with long-range and short-range problems regarding the characteristics of living matter.

The book is well written and mentally stimulating.

J. C. K., JR.

Congenital Malformations of the Heart. By HELEN B. TAUSSIG, M.D., Associate Professor of Pediatrics, The Johns Hopkins University School of Medicine, and Director of the Children's Cardiac Clinic of the Harriet Lane Home of The Johns Hopkins Hospital. 618 pages; 18 × 26 cm. The Commonwealth Fund, 41 East 57th St., New York. 1947. Price, $10.00.

This volume is a valuable addition to the literature on heart disease. There has been no satisfactory book available on congenital heart disease, and it is believed that this exposition will meet the requirements of all interested in such abnormalities. The author shows how to arrive at a correct diagnosis by means available to most physicians. From the history and development of the child, the presence or absence of cyanosis, the physical findings, and extremely important, the fluoroscopic study of the chambers of the heart and the size and pattern of the great vessels, with help from the electrocardiogram in certain conditions, she logically deduces the main pattern of the defect. Methods such as catheterization of the heart and x-ray studies following the injection of a radio-opaque dye are described, but are not stressed as being necessary to come to an understanding of the lesion at hand. The author points out that the clinical diagnosis of congenital lesions is often not possible in early infancy, but must await the development of the heart in the post natal period. The chapter on "The Physiology of the Malformed Heart and Diagnostic Principles" is excellent; and indeed much of the latter can be applied to the diagnosis of heart lesions in adults. Surgical treatment of coarctation of the aorta, persistent ductus arteriosus, and pulmonic stenosis are discussed.

The book is well illustrated by understandable diagrams of the circulation in the various lesions discussed, x-rays, and photographs and drawings of pathological specimens. It is highly recommended. The publishers have also done an excellent piece of work, and it is a pleasure to read such a well set up volume.

W. S. L.

BOOKS RECEIVED

Books received during January are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Autoxidation of Diethyl Ether and Its Inhibition by Diphenylamine: A chemical, biological and clinical study of some practically important problems concerning the protection of anesthetic ether against disintegration. By GUNNAR LINDGREN. 190 pages; 23 × 14.5 cm., paper bound. 1946. Acta Chirurgica Scandinavica, c/o Norstedt & Soner, Stockholm 2. Price, 12:– Swedish crowns.

Blood Pressure and Its Disorders, Including Angina Pectoris. 2nd Ed. By JOHN PLESCH, M.D., Budapest, etc. 307 pages; 22.5 × 14.5 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, $6.00.

Cardiopatias Congenitas de la Infancia. By DR. AGUSTIN CASTELLANOS Y GONZALEZ, Profesor Agregado de la Catedra de Patologia y Clinica Infantil de la Universidad de la Habana, with the collaboration of DR. L. A. CABRERA. 406 pages (and atlas); 23.5 × 16 cm. 1948. Manuel V. Fresneda, Havana. Price, $9.00.

Diabetes Mellitus in General Practice. By ARTHUR R. COLWELL, M.D., Associate Professor of Medicine and Director of Medical Specialty Training, Northwestern University Medical School, etc. 350 pages; 21 × 14.5 cm. 1947. Year Book Publishers, Inc., Chicago. Price, $5.25.

Diseases of the Joints and Rheumatism. By KENNETH STONE, D.M. (Oxon.), M.R.C.P., Honorary Physician, B.R.C.S. Clinic for Rheumatism, London, etc. 362 pages; 23.5 × 16 cm. 1947. Grune & Stratton, Inc., New York. Price, $6.50.

Endocrine Therapy in General Practice. 6th Ed. By ELMER L. SEVRINGHAUS, M.D., F.A.C.P., Formerly Professor of Medicine, University of Wisconsin, etc. 264 pages; 21 × 14.5 cm. 1948. Year Book Publishers, Inc., Chicago. Price, $4.00.

Experimental Air-Borne Infection: Equipment and Methods for the Quantitative Study of Highly Infective Agents; Basic Data on Their Use Obtained with Phenol Red, Serratia Marcescens and Bacillus Globigii; and Preliminary Experiments on the Stability and Infectivity for Laboratory Animals of Air-Borne Clouds of Brucella Suis, Malleomyces Mallei, Malleomyces Pseudomallei, Pasteurella Tularensis, and of Viruses of the Psittacosis Group. By THEODOR ROSEBURY, with the co-authorship and assistance of the staff of the Laboratories of Camp Detrick, Maryland. 222 pages; 23.5 × 15.5 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, $4.00.

Illustrative Electrocardiography. 3d Ed. By JULIUS BURSTEIN, A.B., M.D., Visiting Electrocardiographer and Chief of the Cardiac Clinic, Morrisania City Hospital, New York, etc., and NATHAN BLOOM, M.D., F.A.C.P., Associate Professor of Medicine and Chief of the Department of Electrocardiography, Medical College of Virginia, Richmond. 309 pages; 24.5 × 16 cm. 1948. D. Appleton-Century Company, New York. Price, $6.00.

An Introduction to Gastro-enterology: A Clinical Study of the Structure and Functions of the Human Alimentary Tube. By JAMES DUNLOP LICKLEY, M.D., Hon. Consulting Physician, Sick Children's Hospital, Newcastle-upon-Tyne, etc. 143 pages; 19 × 12.5 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, $3.00.

Medicine: Volume I—The Patient and His Disease. By A. E. CLARK-KENNEDY, M.D., F.R.C.P., Fellow of Corpus Christi College, Cambridge, etc. 383 pages; 24.5 × 15.5 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, $6.00.

Sexual Behavior in the Human Male. By ALFRED C. KINSEY, Professor of Zoology, Indiana University; WARDELL B. POMEROY, Research Associate, Indiana University, and CLYDE E. MARTIN, Research Associate, Indiana University. 804 pages; 24 × 16 cm. 1948. W. B. Saunders Company, Philadelphia. Price, $6.50.

Tercer Congreso Interamericano de Cirugia: Tomo III. Presidente: DR. DOMINGO PRAT. 662 pages; 24.5 × 17 cm. 1946 (October). Secretaria: Agraciada 1464 —Piso 13.

Tercer Congreso Interamericano de Cirugia: Tomo II. Presidente: DR. DOMINGO PRAT. 582 pages; 24.5 × 17 cm. 1946 (October). Secretaria: Agraciada 1464 —Piso 13.

The Treatment of Rheumatism in General Practice. 4th Ed. By W. S. C. COPEMAN, O.B.E., M.A., M.D. (Cantab.), F.R.C.P. (London), Physician in Charge, Department of Chronic Rheumatic Diseases, West London Hospital. 258 pages; 22.5 ×14.5 cm. 1946. The Williams & Wilkins Company, Baltimore. Price, $4.00.

Treatment of Some Chronic and 'Incurable' Diseases. 2nd Ed. A. T. TODD, O.B.E., M.B. (Edin.), M.R.C.P. (Lond.), Honorary Physician, Bristol Royal Infirmary. 324 pages; 22.5 × 14.5 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, $7.00.

COLLEGE NEWS NOTES

Nominations for A.C.P. Elective Offices, 1948–49

In accordance with the By-Laws of the American College of Physicians, Article I, Section 3, the following nominations for the elective offices, 1948–49, are herewith announced and published:

President Elect ..... Reginald Fitz, Boston, Mass.
First Vice President ..... William S. Middleton, Madison, Wis.
Second Vice President ..... Maurice C. Pincoffs, Baltimore, Md.
Third Vice President ..... Charles E. Watts, Seattle, Wash.

Regular elections will take place at the 1948 Annual Session in San Francisco, April 19–23. The Annual Business Meeting will be held Thursday afternoon, April 22, in Polk Hall of the Civic Auditorium.

The election of nominees shall be by the Fellows and Masters of the College. The above nominations do not preclude other nominations made from the floor at the Business Meeting.

Nominations for members of the Board of Regents and Board of Governors will be presented at the Business Meeting, as provided in the By-Laws.

Respectfully submitted,
Walter B. Martin, Norfolk, Va.
Edgar V. Allen, Rochester, Minn.
George H. Lathrope, Newark, N. J.
Edward L. Turner, Seattle, Wash.
William D. Stroud, Chairman, Philadelphia, Pa.
Committee on Nominations

Additional Life Members

The American College of Physicians announces that the following Fellows became Life Members of the College by recent subscription:

Julius Bauer, Los Angeles, Calif.
David Beck, New York, N. Y.
Reuben Berman, Minneapolis, Minn.
Wyndham B. Blanton, Richmond, Va.
Meyer Bloom, Johnstown, Pa.
T. Homer Coffen, Portland, Ore.
Charles Cramer, Jackson Heights, N. Y.
Joseph S. D'Antoni, New Orleans, La.
Harold Freed, Dallas, Tex.
John L. Gompertz, Oakland, Calif.
Alfred S. Hartwell, Honolulu, T. H.
James H. Herndon, Dallas, Tex.
Byron J. Hoffman, Atlanta, Ga.
L. Winfield Kohn, New York, N. Y.
Abbe A. Ledbetter, Houston, Tex.
Harry R. Lipton, Atlanta, Ga.
William L. Lowrie, Jr., Detroit, Mich.
Warren S. Lyman, Ottawa, Ont., Can.
Willard Machle, New York, N. Y.
Jerome A. Marks, New York, N. Y.

Ralph McReynolds, Quincy, Ill.
Leo J. Meienberg, Portland, Ore.
Murlin P. Merryman, Rapid City, S. D.
Carlisle Morse, Louisville, Ky.
Max K. Newman, Detroit, Mich.
Lawrence Parsons, Reno, Nev.
Abraham Penner, New York, N. Y.
Lawrence E. Putnam, Washington, D. C.
Marjorie E. Reed, Plymouth, Pa.
Harold E. Richardson, St. Paul, Minn.
Andrew S. Robinson, Akron, Ohio
Percy K. Smith, Wichita Falls, Tex.
Robert L. Smith, Jr., San Francisco, Calif.
William H. Stoner, Bloomfield, N. J.
Robert T. Sutherland, Oakland, Calif.
Walter C. Swann, Huntington, W. Va.
Herman Tarnower, Scarsdale, N. Y.
Frederick R. Taylor, High Point, N. C.
A. M. Wehenkel, Detroit, Mich.
Sumner M. Wells, Jr., Grand Rapids, Mich.
Charles P. Wilson, Portland, Ore.
McIver Woody, New York, N. Y.
Paul H. Wosika, Chicago, Ill.

Fellowship in Allergy Available at Northwestern University

The Division of Allergy, Northwestern University Medical School, announces a fellowship for training in allergy. Candidates should have experience in research or in basic sciences. The Fellow will receive training in clinical allergy and in research and may register for an M.S. degree. This training is approved by the various Boards and by the Council on Medical Education and Hospitals of the A. M. A. Stipend is from $1800 to $3000. A similar training, without stipend, is also offered to a candidate whose qualifications do not meet fellowship requirements. For information address Dr. Samuel M. Feinberg, Northwestern University Medical School, Chicago, Ill.

International Congress on Mental Health

The International Committee for Mental Hygiene is sponsoring a congress in London, England, August 11–21, 1948, which will feature three conferences, the first concerning child psychiatry, having as its theme personality development with special reference to aggression. The second conference will deal with medical psychotherapy with reference to guilt. These two conferences will occur August 11 to 14. The third conference, August 16–21, will concern mental hygiene and have as its theme mental health and world citizenship. A primary purpose of the Congress is to facilitate the exchange of scientific knowledge and experience which was acquired during the war, in social studies. There will be from 1000 to 2000 participants from many countries of the world; more than 500 are expected to come from the United States. For an effective congress involving so many scientists it has been found necessary to arrange for discussion groups to outline the program in advance. There are 83 such groups presently at work in the United States and 50 in other countries.

An International Preparatory Commission is planned which will meet before the Congress to receive reports from the discussion groups and to prepare recommenda-

tions which may be adopted by the Congress for submission to the World Health Organization and UNESCO.

Membership is open to trained workers in mental health and related subjects. The Executive Officer is Nina Ridenour, Ph.D., International Committee for Mental Hygiene, Inc., 1790 Broadway, New York 19, N. Y. Jonathan C. Meakins, M.D., F.A.C.P., Montreal, is Vice President of the organization and Henry W. Brosin, M.D., F.A.C.P., Chicago, C. Charles Burlingame, M.D., F.A.C.P., Hartford, Conn., and William C. Menninger, M.D., F.A.C.P., Topeka, Kans., are members of the Governing Board.

The Mississippi Valley Medical Society, of which Willard O. Thompson, M.D., F.A.C.P., Chicago, Ill., is President, will hold its 1948 annual meeting, September 29 to October 1 at Springfield, Ill.

The Joint Committee for the Coördination of Medical Activities, of which Ernest E. Irons, M.D., F.A.C.P., is Chairman, met in Chicago, December 6, 1947. The Committee discussed the following subjects: Navy training for medical aides in the Pacific Islands, school health and physical education program, problems affecting the general practitioner, pending legislation affecting medical practice, the Hospital Survey and Construction Program, nursing problem, rural medical service, World Medical Association, graduate education for medical officers, surplus war medical supplies, and outbreaks among the new-born in hospitals. The minutes of meetings of the Joint Committee are published in full periodically in The Journal of the American Medical Association.

American Overseas Aid is a federation of major voluntary foreign relief agencies which has been designated by President Truman to handle American participation in the world-wide United Nations Appeal for Children. Thus the one campaign for $60,000,000 beginning in February, will provide funds for 24 private overseas relief agencies and the International Children's Emergency Fund, the United Nations agency which will administer funds collected by the United Nations Appeal for Children.

Recent Regional Meetings

Southern California, Los Angeles, January 23, 1948. A formal dinner meeting was arranged by the local Governor, Leland P. Hawkins, M.D., F.A.C.P., at the California Club. Lee A. DuBridge, President of the California Institute of Technology, was the guest speaker; his subject was "Science and the Future."

Virginia, Charlottesville, February 12, 1948. This meeting was held under the chairmanship of Staige D. Blackford, M.D., F.A.C.P., President of the Virginia section of the College. The following papers were presented in the afternoon session at the University of Virginia: "Recent Advances in Etiology and Therapy of Portal Cirrhosis," by H. B. Mulholland, M.D., F.A.C.P., and Thomas S. Edwards, M.D.;* "Effect of Fever on Liver Function," by Byrd S. Leavell, M.D., F.A.C.P., and Myer Hicks, M.D.;* "Electrophoretic Studies in Heart Disease," by Preston B. Lowrance, M.D.,* and Alfred Chanutin, M.D.;* "Relative Rates of Renal Excretion of Sodium and Chloride Ions in Normal, Heart Failure and Hypertensive Subjects," by Andrew J. Crutchfield, M.D.,* and J. Edwin Wood, Jr., M.D., F.A.C.P., College Governor for Virginia; "Use of Curare in Muscular Spastic States," by Walter Klingman, M.D., F.A.C.P.; "Psychosomatic Treatment," by Andrew D. Hart, Jr., M.D., F.A.C.P.;

* By invitation.

"Lipid Studies in Disease," by H. Rowland Pearsall, M.D.,* and Alfred Chanutin, M.D.;* "Effects of Nitrogen Mustards on Hematopoietic Organs," by J. E. Kindred, M.D.;* "Treatment of Leukemia with Urethane," by Howard P. Holt, M.D.,* and Byrd S. Leavell, M.D., F.A.C.P.; "Chemical Composition of Thymoma," by Thomas N. Warren, M.D.,* and Alfred Chanutin, M.D.* A reception and informal dinner at the Farmington Country Club followed the scientific session.

Texas, Arkansas, Louisiana, Mississippi and *Tennessee,* Houston, Tex., February 27 and 28, 1948. This was the first Regional Meeting to be held in Texas. The College Governors for the participating states presided over the sessions. Dr. Hugh J. Morgan, President of the College, addressed the dinner meeting on February 27 on the subject, "The Rôle of the American College of Physicians in American Medicine," and conducted a clinical-pathological conference the next day. Papers were presented by the following physicians: Julius H. Comroe, Jr., F.A.C.P., Philadelphia, Pa., "New Autonomic Drugs"; Oliver C. Melson, F.A.C.P., Little Rock, "Differential Diagnosis of Upper Abdominal Lesions"; Charles T. Stone, F.A.C.P., Galveston, "Infectious Hepatitis"; Edwin L. Rippy, F.AC.P., Dallas, "Perpetuation of Psychosomatic Disorders by the Physician"; John K. Thompson, Associate, Fort Smith, "Congenital Toxoplasmosis"; Daniel E. Jenkins, Associate, Houston, "Streptomycin in the Treatment of Certain Forms of Tuberculosis"; Douglas H. Sprunt, F.A.C.P., Memphis, "The Effect of Nutrition on Viral Diseases"; Lucian M. Ferris, Associate, and T. H. Martin,* Vicksburg, "Use of Sympathetic Nerve Blocks in the Ambulatory Patient"; Samuel A. Shelburne, F.A.C.P., Dallas, "Long-term Study of Retinal Vessels in Hypertensive Patients"; A. Gayden Ward, F.A.C.P., Jackson, "Patent Ductus Arteriosus—A Report of Three Cases Successfully Treated by Surgery"; Don W. Chapman, Associate, Houston, "Venous Catheterization of the Heart in the Diagnosis of Congenital Heart Diseases"; G. M. Anderson,* New Orleans, "Prevention of Thrombo-Embolic Complications in Congestive Heart Failure"; Raymond L. Gregory, F.A.C.P., Galveston, "Unusual Diseases Affecting the Kidney"; William L. Marr, F.A.C.P., Galveston, "Refractory Anemias"; R. A. Hettig,* Houston, "Nitrogen Mustard Therapy in Blood and Lymph Dyscrasias." Chairmen of the Program and Arrangements Committees were James A. Greene, F.A.C.P., and DeWitt H. Hotchkiss, Jr., Associate, respectively, of Houston.

* By invitation.

OBITUARIES

DR. CLARENCE ORION CHENEY

Clarence Orion Cheney, M.D., F.A.C.P., died November 4, 1947, at White Plains, N. Y., at the age of 60. A well-known psychiatrist and former president of The American Psychiatric Association, he had been a Fellow of The American College of Physicians since 1939.

Dr. Cheney was born in Poughkeepsie, N. Y., July 10, 1887. He received the A.B. degree from Columbia University in 1908, and the M.D. degree from the College of Physicians and Surgeons, Columbia University, in 1911. Following an internship at Manhattan State Hospital, he was appointed Assistant Physician and Pathologist at that hospital from 1912 to 1917. From 1917 to 1922 he served as Assistant Director of the New York State Psychiatric Institute and Hospital in New York City. In 1922 he became Assistant Superintendent of the Utica State Hospital and in 1926 was appointed Superintendent of the Hudson River State Hospital at Poughkeepsie, N. Y. He left this post in 1931 to accept The Directorship of the New York State Psychiatric Institute and Hospital. Leaving the New York State service after twenty-five years, he became Medical Director of the New York Hospital, Westchester Division, in White Plains, N. Y., in 1936, which position he resigned in 1946. Throughout this period of thirty-five years of association with psychiatric hospitals he maintained a vigorous interest in studies of their problems, in teaching and in research. At Manhattan State Hospital he had done research in epilepsy, cerebral arteriosclerosis, on the spirochetae pallidae in the brains of paretics and on nerve cell changes in dementia praecox. At the New York State Psychiatric Institute he did special research in the relation of focal infection to mental disorders, and in his posts as administrator and director was a stimulating influence upon his staff in carrying out numerous research projects.

He was a successful and interested teacher, accepting appointment as Instructor in Psychiatry at Cornell University Medical College in 1914 where he was also Attending Physician and Chief of Clinic at The Cornell Dispensary. From 1917 to 1918 he was Instructor in Psychiatry at New York University and Bellevue Medical School, giving the entire course in Psychiatry both at Cornell Medical College and this school during that war year. In 1922, while at the Utica State Hospital he served as Instructor in Psychiatry at Syracuse University Medical School and was Attending Physician at the Utica Free Dispensary. When he went to Poughkeepsie in 1931, he became Professor of Clinical Psychiatry at the College of Physicians and Surgeons, Columbia University, and in 1932 Professor of Clinical Psychiatry and Executive Officer of the department at the same college. From 1935 to 1936 he was Representative of the Medical Faculty on the University Council at Columbia University. Upon his resignation from state appointments and acceptance of the Directorship at the New York Hospital Westchester Division, he became Professor of Clinical Psychiatry at Cornell University Medical College which position he held until his death.

He was an organizer and charter member of The American Board of Psychiatry and Neurology and was certified by this Board in 1934. He was certified as a Qualified Psychiatrist by the Board of Psychiatric Examiners of The New York State Department of Mental Hygiene in 1937, and was Representative of The New York State Medical Society on this Board of Examiners since 1944. He also served on various special commissions on hospital, sociological and post-war planning problems. Active as a member of the local Draft Board in New York City in World War I, he was Psychiatrist to the Medical Advisory Board of Westchester County during World War II, and at the time of his death was Consultant in Psychiatry to the Veterans Administration in New York City.

He participated actively in local and national medical societies, serving as Secretary and Treasurer of The American Psychiatric Association from 1928 to 1933, and as President in 1935–36. From 1933 to 1935 he was President of the New York Society for Clinical Psychiatry and served as Secretary and Chairman of the Section on Neurology and Psychiatry of The New York State Medical Society. In 1927–28 he was elected President of the Dutchess County Medical Society and was Chairman of the Committee on Mental Health from 1937 to 1942 of the Westchester County Medical Society. He was also an honorary member of The Southern Psychiatric Association, and corresponding member of the Royal Medico-Psychological Association of England.

He was Consulting Psychiatrist to seven hospitals, was a member of the White Plains Rotary Club, University Club, Sigma Xi and Alpha Omega Alpha.

In addition to this active participation in psychiatric progress, he found time to act as Associate Editor of The American Journal of Psychiatry from 1931, and as Associate Editor of The Psychiatric Quarterly from 1933.

The loss of Dr. Cheney will be deeply felt by the psychiatric profession and particularly by his many friends and former students.

CURTIS T. PROUT, M.D., F.A.C.P.

DR. WILLIAM PEPPER

Dr. William Pepper, Dean Emeritus of the University of Pennsylvania School of Medicine, died December 3, 1947, at the age of 73.

Dr. Pepper retired two years ago after serving as Dean of the Medical School for 33 years. His death was attributed to coronary thrombosis. He was the third William Pepper to serve the University of Pennsylvania in a distinguished position. His grandfather held the chair of theory and practice of medicine from 1860 to 1864, and his father was provost and professor of medicine from 1881 to 1894. Dr. Pepper was a cousin of the former U. S. Senator George Wharton Pepper and a direct descendant of Benjamin Franklin. He held the degrees of A.B., M.D., and D.Sc., from the University of Pennsylvania and an honorary doctorate of laws from Temple University. He contributed many articles to leading medical journals and was a member of many scientific societies and a former President of the Association of American Medical Colleges. He was also a trustee of the University of Pennsylvania. He is survived by two sons, William Pepper, Jr., an officer of the Philadelphia Free Library, D. Sergeant Pepper, M.D., F.A.C.P., Assistant Medical Director of the Provident Mutual Life Insurance Company, a daughter, Mrs. Mary Pepper Parker, and a brother, O. H. Perry Pepper, M.D., M.A.C.P., Professor of Medicine in the University of Pennsylvania.

All of the many who knew Dean Pepper will recall the sympathetic and good humored interest with which those who consulted him were received, and the absolute integrity which even the most casual acquaintance perceived in him. His long and distinguished career covered a vital period of transition in medical education. In his passing American medicine has lost one of its links with the past.

DR. RICHARD RAY DALRYMPLE

Dr. Richard Ray Dalrymple, F.A.C.P., died in the Warren General Hospital, Warren, Pa., on October 19, 1947. Dr. Dalrymple was born at Warren, Pa., on June 4, 1891, attended the local public schools, Bellefonte Academy, and received his medical degree from Jefferson Medical College of Philadelphia in 1920. He was in the practice of internal medicine at Erie, Pa., for several years and then removed to Fond du Lac, Wis., and thereafter, at the opening of World War II, he entered the Medical Corps of the U. S. Army, advancing to the rank of Lieutenant Colonel. His death was due to tuberculosis. He had been a Fellow of the American College of Physicians since 1929.

DR. GEORGE HERBERT EVANS

Dr. George Herbert Evans was born in Ontario, Can. He came to the United States in his early years. After finishing public schools he took his medical degree at Detroit College of Medicine and Surgery in 1891. He went immediately to San Francisco and began the practice of his profession, which he continued until his retirement in 1933.

He possessed elements of leadership which he showed in many ways. He early became interested in tuberculosis, and gave it much of his time, although he considered internal medicine his field of practice.

In 1903, the Medical Society of the State of California appointed a committee to study the question of tuberculosis in the state. Dr. Evans was a member of that committee. It worked in harmony with the Southern California Antituberculosis League which had been established the year before, the chief aim of which was educational and organizational.

It was under the auspices of the state committee, in 1904, that Dr. Evans called the meeting at which the San Francisco Tuberculosis Association was formed. He was active in local, state, national and international tuberculosis associations. He was active in forming the California Tuberculosis Association and served as its president in 1912. He was a delegate to the Fifth International Tuberculosis Congress in Paris in 1905, and the Sixth, in Washington in 1908.

He was active in the formation of and was Director of the "Tuberculosis Colony," instituted by the San Francisco Department of Health in 1906, the first attempt of the city to isolate those suffering from active tuberculosis.

He was an active member of many medical societies, and served as Secretary of the Medical Society of the State of California in 1903. He was a past President of the San Francisco County Medical Society, the Medical Society of the State of California, the California Academy of Medicine, the American Therapeutic Society, and the California Tuberculosis Association; and a Fellow of the American Medical Association and the American College of Physicians.

In 103 he was a member of the "Health Committee" which was instrumental in securing an unwilling coöperation on the part of the state and municipal authorities to recognize the presence of plague in the city and to initiate steps for its eradication and future prevention.

In 1913 he was appointed Assistant Clinical Professor of Medicine in the University of California, and organized the Department of Tuberculosis. He was an active teacher until 1933.

After his retirement he spent much time abroad, particularly in England and Italy, studying tuberculosis, housing, archeology, and medical history. He published an unusually interesting description of a visit to Harvey's tomb. He had compiled many notes which were to serve as the basis for future contributions. His study of the early history of tuberculosis in California shows that the first mention of tuberculosis among the settlers was among the Russians who came down from Alaska and settled along the northern California coast.

Dr. Evans had wide interests, was a good conversationalist, and a charming companion. He was a member of the Bohemian Club and the Commonwealth Club of San Francisco, and the Author's Club of London.

In April, 1947, he received one of the first medals awarded by the California Tuberculosis and Health Association for outstanding service in the cause of tuberculosis.

Dr. Evans died of a cerebral hemorrhage September 5, 1947, in his seventy-eighth year, after a full life of accomplishment.

F. M. Pottenger, M.D., F.A.C.P.,
Monrovia, Calif.

COLONEL JOHN T. AYDELOTTE

Colonel John T. Aydelotte, a Fellow of the American College of Physicians since 1930, died July 5, 1947, in Brooke General Hospital, Fort Sam Houston, Tex., where he had been taken from his home in San Antonio.

Born August 28, 1884, in Ocean City, Md., he was graduated from Jefferson Medical College of Philadelphia in 1906. He joined the Medical Reserve Corps of the Army on September 1, 1909, and after graduating from the Army Medical School, Washington, D. C., in 1910, was commissioned a First Lieutenant in the Medical Corps, Regular Army, May 8, 1910. The next fifteen months were spent at Fort Sam Houston, and then he was sent to the Philippine Islands for a normal tour of duty. He spent the next four years in various camps and posts in California, Wyoming, Texas and Arizona. In June, 1918, he became Camp Surgeon at Camp MacArthur, Tex.

After a period of instruction at Army War College, Washington, D. C., and a year's service in camps in Alabama, Mississippi, and Kentucky, he was sent to General Hospital No. 11, Camp May, N. J., for special instruction in the diagnosis and treatment of peripheral nerve injury cases. Then he became Chief of the Neuropsychiatry Section at General Hospital No. 6, Fort McPherson, Ga.

When the R.O.T.C. Unit was established at Jefferson Medical College of Philadelphia, Colonel Aydelotte was chosen as a Professor of Military Science and Tactics there, and the success of that unit was due largely to his tact, personality, and good judgment, which won friends for himself and the unit from the very beginning.

He also served as Surgeon at Fort Slocum, N. Y., and, after four years at Fitzsimons General Hospital, Denver, Colo., was sent to China. He was retired from the service at Fort Devens, Mass., May 31, 1936.

DR. EDWARD JOHN KEPLER

Edward John Kepler, M.D., F.A.C.P., of Rochester, Minn., died October 19, 1947. He had known for many months that he was seriously ill with coronary arteriosclerosis.

Dr. Kepler, a graduate of the University of Minnesota Medical School, was born at Erie, Pa., January 22, 1894. He received the B.S. degree from Pennsylvania State College in 1916, and the M.B., M.D. and M.S. degrees from the University of Minnesota subsequently. Following an internship in the Philadelphia General Hospital, Dr. Kepler was appointed Fellow in Medicine in the Mayo Foundation in 1925. He rose to become Professor of Medicine in the University of Minnesota (Mayo Foundation), and Associate in Medicine in the Mayo Clinic. He was a diplomate of the American Board of Internal Medicine.

Dr. Kepler became a Fellow of the American College of Physicians in 1938. He was also a Fellow of the American Medical Association, and a member of the Olmsted-Houston-Fillmore-Dodge Counties Medical Society, the Central Society for Clinical Research and the Association for the Study of Internal Secretions.

Dr. Kepler was a physician with intense curiosity about the unknown in medicine; almost every patient raised problems in his mind which were outside ordinary medical thinking. His philosophic approach to medical problems and to life in general endeared him to his colleagues and students. His death removed from medical circles one of those rare individuals with really great minds and, from his circle of friends, a beloved individual.

E. V. Allen, M.D., F.A.C.P.,
Governor for Minnesota

DR. H. MILTON CONNER

H. Milton Conner, M.D., F.A.C.P., of Rochester, Minn., died October 18, 1947, at the age of 66 years; for several years prior to his death he had been confined to bed, a victim of severe Parkinson's disease. He is remembered by his associates in the Mayo Clinic and the Mayo Foundation as a valued friend and as a splendid clinician who had the welfare of his patients foremost in his mind.

A graduate of the Kansas Medical College, Topeka, Dr. Conner served that school from 1910 to 1913 as Professor of Pathology. He later joined the staff of the Mayo Clinic as Consulting Physician, and held appointment in the University of Minnesota (Mayo Foundation) as Associate Professor of Medicine. He was a diplomate of the American Board of Internal Medicine.

Dr. Conner was a member of the Olmsted-Houston-Fillmore-Dodge Counties Medical Society, of the Minnesota State and Southern Minnesota Medical Associations, Minnesota Society of Internal Medicine, Central Society for Clinical Research, and the Societe Francaise d'Hematologie. He was a Fellow of the American Medical Association, and, since 1922, of the American College of Physicians.

E. V. Allen, M.D., F.A.C.P.,
Governor for Minnesota

DR. JAMES ANDREW FOUNTAIN

James Andrew Fountain, M.D., F.A.C.P., of Macon, Ga., died June 26, 1947, following a heart attack. He was 54 years of age.

Dr. Fountain, who graduated from Vanderbilt University School of Medicine in 1917, was a veteran of World War I, when he served as a medical officer in the Navy. He practiced medicine in Macon for 26 years. He was a member of the Bibb County Medical and Georgia State medical societies. He had been a Fellow of the American College of Physicians since 1931.

Glenville Giddings, M.D., F.A.C.P.,
Governor for Georgia

DR. MARGARET ANN GOULD

Dr. Margaret Ann Gould, an Associate member of the College since 1925, and a competent and sympathetic practitioner, died October 30, 1947. Quiet and modest, and always faithful to her responsibilities, Miss Gould had a host of friends, as well as loyal patients who counted on her for tactful guidance and professional care.

Born in 1870, Dr. Gould received her medical training at Trinity Medical College, Toronto, in 1898. She interned at the Women's Hospital in Philadelphia, and took up general practice in Pittsburgh in 1903.

After a career of great usefulness she retired in May, 1941, and spent her winters thereafter in Florida. Dr. Gould was one of the first of the women physicians to practice in Pittsburgh. Her attractive personality, combined with kindness, tact, and unselfish devotion to her duties, won her the cordial coöperation and respect of her colleagues.

R. R. Snowden, M.D., F.A.C.P.,
Governor for Western Pennsylvania

DR. FREDERICK JOHN POHLE

In the premature death of Frederick John Pohle on November 26, 1947, the American College of Physicians lost one of its most promising young members, and the University of Wisconsin Medical School a most valued investigator and teacher.

Dr. Pohle was born on May 1, 1906, at Bloomington, Wis., where he received his early education in the public schools. Later, after attending the La Crosse Normal

School, he taught in the Waukesha High School for one year before entering the University of Michigan where he received the degree of Doctor of Medicine in 1934. He then came to the State of Wisconsin General Hospital as an intern and assistant resident in medicine. From 1936 to 1938 he was a research fellow at Harvard Medical School and an assistant resident in medicine at the Thorndike Memorial Laboratory, Boston City Hospital. He returned to the University of Wisconsin Medical School in 1938 as a research associate; from 1940 to 1946 he was assistant professor of medicine, and physician to the State of Wisconsin General Hospital.

In January, 1941, he was activated as a Major with the 135th Medical Regiment, Wisconsin National Guard. He was later transferred to Station Hospital, Fort Bragg, N. C., where he served as Chief of Laboratory Service, with rank of Lieutenant Colonel, until his retirement from the Medical Corps of the Army of the United States in 1945.

Following his return to the University of Wisconsin Medical School, he was advanced to the rank of associate professor of medicine in 1946. He held this appointment at the time of his death, which followed an operation for subarachnoid hemorrhage.

Dr. Pohle's interest in medical research began when, as a medical student, he assisted in hematological research at the Simpson Memorial Institute. He published many authoritative papers subsequently, gaining for himself a national and international reputation, especially in the field of hematology. Recognition came to him through membership in many nationally important scientific societies, including Alpha Omega Alpha, Sigma Xi, The American Society for Clinical Investigation, The Central Society for Clinical Research, the Central Clinical Research Club. He was a diplomate of the American Board of Internal Medicine, and was elected an Associate of the American College of Physicians in October, 1946. He was also a member of the Dane County and Wisconsin Medical Societies, and a fellow of the American Medical Association.

Dr. Pohle is survived by his widow and their two daughters. The College extends its sympathy to them, and shares in their loss of husband, father, investigator, author, teacher and clinician.

KARVER L. PUESTOW, M.D., F.A.C.P.,
Governor for Wisconsin

DR. HAROLD IRWIN REYNOLDS

Harold Irwin Reynolds, M.D., F.A.C.P., of Athens, Ga., died on October 30, 1947, of chronic lymphatic leukemia.

Born at Lexington, Ga., in 1887, Dr. Reynolds obtained his medical degree in 1912 from the Johns Hopkins University School of Medicine; he had previously attended the University of Georgia and had received from it the degree of Bachelor of Arts. He subsequently served his alma mater as University Physician, in charge of the Crawford W. Long Infirmary. He was also a member of the medical staffs of the Athens General and St. Mary's Hospitals, and was regarded as an outstanding physician in the section of Georgia in which he practiced internal medicine.

Dr. Reynolds was a member of the Clarke-Madison-Oconee Counties and Eighth District Medical Societies, the Medical Association of Georgia and the Southern and American Medical Associations. He was elected to Fellowship in the American College of Physicians in 1927.

DR. COLIN GEORGE SUTHERLAND

On November 12, 1947, in his fifty-fifth year, death came suddenly to Dr. Colin G. Sutherland, Assistant Professor of Medicine in the McGill University Faculty of Medicine, and Physician to the Royal Victoria Hospital, in Montreal.

Born in Nova Scotia, and educated at Dalhousie University (B.A., 1913), he qualified as M.D., C.M. at McGill in 1917, serving in the Canadian Army Medical Corps in World War I prior to and after graduation. This was followed by a two year internship at the Royal Victoria Hospital, with Dr. Charles F. Martin in Medicine and, in Surgery and Urology, with Dr. A. E. Garrow and Dr. David MacKenzie, respectively. He then proceeded to the Johns Hopkins Hospital in Baltimore for a year with Dr. Tom Brown in Gastro-enterology, and subsequently returned to Montreal to enter practice with major interest in this specialty, and to join the hospital and teaching staffs of the Royal Victoria Hospital and McGill University.

During the late war, Dr. Sutherland served as Medical Consultant to the Department of Veterans Affairs and also had supervision of medical cases in the soldiers' ward, a responsibility which he discharged with characteristic efficiency and unremitting care.

He was a member of the Montreal Medico-Chirurgical Society, the Canadian Medical Association, and a Fellow of the American Gastro-Enterological Association. He was elected a Fellow of the American College of Physicians in 1931.

Forthright, vigorous, vital, sometimes refreshingly outspoken, he was intolerant of all insincerity and dissembling. He was implicitly trusted by his colleagues and patients, and warmly loved by his friends. Characteristic also was an infectious optimism which endeared him to many of his patients, enduing them as it did with patience and courage to hope and to endure. An ardent golfer, and an enthusiastic curler (fortunately they did not conflict) nevertheless his chosen profession and its heavy demands upon his time and energy were always paramount.

ARTHUR T. HENDERSON, M.D., F.A.C.P.,
Governor for Quebec

DR. BENJAMIN JAFFEE BIRK

Benjamin Jaffee Birk, M.D., F.A.C.P., was born in Michigan City, Ind., on August 17, 1894. He received his B.S. degree from the University of Indiana in 1916 and his M.D. degree from Rush Medical College in 1919. He then served interneships in the Michael Reese and Cook County Hospitals, Chicago. He did postgraduate work at the University of Chicago School of Medicine, and furthered his studies in internal medicine at the University of Vienna in 1927–28.

As a Milwaukee physician for almost thirty years, Dr. Birk served as Chief Resident, Chief of Staff, Head of Division of Medicine, and finally Head of the Department of Internal Medicine of Mt. Sinai Hospital. From 1940 to 1942 he was an Instructor of Internal Medicine in the Marquette University School of Medicine.

During World War I Dr. Birk served in the Army Medical Corps. He was commissioned in the Army of the United States again in 1942 as a lieutenant-colonel. Before going overseas he was chief of medicine at Fort Sheridan, Ill., after which he was attached to the Chinese Combat Command of the United States Army for thirteen months. In 1944, he was awarded the Legion of Merit with oak leaf cluster for especially meritorious conduct. He was discharged in 1946 with rank of colonel.

Dr. Birk was a member of the Military Order of World Wars, Association of Military Surgeons of the United States, Wisconsin Military Association, Reserve Officers Association, American Medical Association, Wisconsin Heart Association, American Heart Association, Milwaukee Academy of Medicine, Milwaukee County and Wisconsin Medical Societies. He had been a Fellow of the American College of Physicians since 1939.

KARVER L. PUESTOW, M.D., F.A.C.P.,
Governor for Wisconsin